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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

W. CRAMER

DeWITT STETTEN

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CONTENTS

The Sex Hormones and the Endocrine Balance . . . 3
W. Cramer

The Blood Plasma for Great Britain Project 27
DeWitt Stetten

Gonorrhea in the Male 39
P. S. Pelouze

Current Trends in Diagnosis of Renal Tuberculosis . 45
John L. Emmett

The Treatment of Renal Tuberculosis 59
William P. Herbst

Gonococcal Infections of Women 64
Robert M. Lewis

Library Notes:
Recent Accessions to the Library 77

Proceedings of Academy Meetings 79

Deaths of Fellows 80

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JANUARY 1941

THE SEX HORMONES AND THE ENDOCRINE BALANCE*

The Middleton Goldsmith Lecture of The New York Pathological Society

W. CRAMER

Research Associate, Barnard Free Skin and Cancer Hospital, St. Louis

Allow me to thank you for honoring me with the invitation to give the Middleton Goldsmith Lecture. Your society is, as far as I know, the oldest pathological society in this continent and one of the oldest, if not the oldest pathological society of the world. It will soon be able to celebrate its centenary. It was founded in 1844 and Middleton Goldsmith, whose bequest established this lecture, was one of its founders together with Lewis A. Sayre and John C. Peters.

When this society was founded, Virchow, who is generally acclaimed as the father of the science of pathology, was twenty-three years old; Pasteur was a year younger, and Lister was a boy of seventeen. New York, where the three founders were young practicing physicians, was at that time a small city ending at what is now 14th Street. Its medical facilities consisted of one college, one hospital, and three dispensaries.

* Given October 4, 1940 at The New York Academy of Medicine.

How did it come about that three young doctors in this environment conceived the idea of founding a pathological society? It is probable that the inspiration came from Vienna though indirectly. Peters had returned from Vienna, where he had come under the influence of Rokitansky, that queer personality who spent his whole working life in the dead house. He is said to have carried out about one thousand autopsies every year for a period of forty years. He and his clinical colleague, Skoda, were then the leaders of the Vienna school, whose ambition it was to establish medicine as an exact science by testing the correctness of every diagnosis by an autopsy, if the patient provided the opportunity. Peters had probably been infected with Rokitansky's enthusiasm for the study of morbid anatomy as the means of advancing medicine, and this bore fruit in the foundation of your society.

But whether the seed that flowered here in little old New York was planted in Vienna or not, to have recognized at that early date the fundamental importance of pathology for the advancement of our knowledge of disease and to have started in this then remote city and without academic support a medical society to be devoted to the exclusive study of a branch of medicine which was just being born in Europe, gives evidence of a far-sighted optimism, so characteristic of this country, which compels our admiration. For this, the names of Middleton Goldsmith and his two co-founders, Sayre and Peters, should be gratefully remembered, and there could not be a more suitable opportunity than this lecture.

In this lecture I wish to lay before you a conception of the interrelationship of the endocrine glands which reveals them as forming functionally one system consisting of a number of units continuously interacting with one another. It is a conception which, while introducing some surprising physiological connections between the different glands, has a special bearing on the still very obscure question of the factors determining the functional activity of the endocrine glands in health and on the even more obscure disturbances of their functional activity as seen by the clinician and the pathologist in disease.

Our interpretation is based on a physiological axiom, which dates back to Claude Bernard, that in a highly differentiated organism the functional activity of the various organs is correlated in such a way as to keep the internal environment constant. More recently the same idea has been expressed by Bordet: "Life is the maintenance of a

balance which is incessantly being disturbed." In this country Cannon has pursued this idea and given to this conception the name "Homeostasis." Cannon as a physiologist emphasizes the maintenance of the balance, Bordet as an experimental pathologist is impressed by its incessant disturbance. In the maintenance of this balance, as in its disturbance, the endocrine organs play a part of outstanding importance. The internal environment is subject to disturbances as a result of changes in the external environment, such as changes in temperature and the intake of food, and also as a result of the activity of the organs, such as muscular movement, and, what is of special interest in its bearing on the problem under discussion, the activity of the endocrine glands themselves. It will be easier to follow the argument if I state our conception now and present the facts and observations which led me to it subsequently. It is, briefly, to regard all the divers endocrine glands as forming one system, in which the individual glands are functionally correlated with each other in varying degrees. This correlation depends upon the direction in which the individual hormones secreted by the endocrine glands affect the internal environment. There are glands the functional activity of which produces a disturbance in the same direction, for example, the thyroid and the adrenal medulla. Such glands are synergists. There are others which when functionally active, produce changes in opposite directions, for example; the islets and the thyroid are antagonists, and so are the islets and the adrenal medulla. In the normal resting organism the internal environment is maintained at its normal level by a balance between the functional activity of the different endocrine glands. If one of these glands is primarily stimulated to functional activity there results a disturbance in the internal environment. In order to restore this to the normal there is a secondary compensatory response in other endocrine glands, which may be of two kinds: the antagonistic gland may show a compensatory increased functional activity, while the synergistic gland may be inhibited. This general pattern is indicated in Table I, in which increased functional activity is indicated by a plus sign, inhibition or dysfunction by a minus sign. When the primary change in an endocrine gland is an inhibition or a dysfunction, produced either by disease or by experimental interference, the secondary compensatory response in other endocrine glands manifests itself in the reverse manner: that is, the antagonists are then inhibited or the synergists are stimulated to increased functional

TABLE I

Primary Change in One Endocrine Gland	Compensatory Change in Antagonist	Compensatory Change in Synergist
+	+	—
—	—	+

activity or both groups of responses occur together.

It is by this arrangement for the maintenance of the internal environment that the functional activities of the divers endocrine glands are interrelated with each other in such a way as to form one system. It may be added that the term antagonist does not imply that all the effects of one hormone are neutralized by the action of its antagonist. The antagonism is only a partial one, and the same is true for the synergism between two glands.

The relationship of the adrenal medulla, the thyroid and the pancreatic islets, which I had investigated in my earlier work[1] offers a good example. The adrenal medulla and the thyroid gland are synergists. They act on the glycogenic function of the liver and on metabolism generally in the same direction, stimulating it. They are stimulated by the same changes in the internal environment, such as exposure to cold, and by the same chemical substances, such as tetrahydronaphthyamine or the toxins of certain bacteria, resulting in the production of fever. Both glands are inhibited in their functional activity by heat. These facts have been established by the method of what one may call functional histology. Functional histology depends on a technique which reveals the functional state of endocrine glands in a direct and incontrovertible manner. It has proved its validity by demonstrating for the first time that the thyroid and the adrenal glands are intimately concerned in the heat regulation of the body and in the etiology of fever.

The effect of insulin, on the other hand, is antagonistic to both thyroxin and adrenalin. It inhibits the glycogenic function of the liver. The antagonism is very evident in relation to the change produced in one feature of the internal environment, the blood sugar. Insulin produces a rapid fall of blood sugar, adrenalin a rapid rise, while thyroxin

produces an increased supply of blood sugar which is oxidized pari passu with the increased supply. The fall of blood sugar produced by an injection of a moderate dose of insulin elicits a compensatory activity of the adrenal medulla which by secreting adrenalin tends to restore the blood sugar to normal. The secretion of adrenalin under this condition, which can be demonstrated by the method of functional histology, is not due to a direct stimulating effect of insulin on the adrenal medulla. For, if insulin is injected together with glucose, so that the fall of blood sugar is avoided and the internal environment is not disturbed, the secretion of adrenalin does not occur. We have here an example of one of the conditions which stimulate the functional activity of an endocrine gland, in this case the adrenal medulla, as a secondary compensatory response to the disturbance of the internal environment produced by the functional activity of its antagonist–in this case the pancreatic islets.

The antagonism between the islets on the one hand and the thyroid-adrenal-medullary apparatus on the other can be demonstrated also from the opposite direction. Any condition which arouses the functional activity of the thyroid or of the adrenal medulla, such as exposure to cold, makes the organism more resistant to the effects of insulin and conversely anything which inhibits the thyroid or adrenal medulla, such as exposure to heat, makes the organism more sensitive to insulin. This relationship is now clearly recognized in the biological assay of insulin in mice, where it is necessary to keep the animals in a constant, warm environment in order to obtain reliable results. This argument applies also to pathological conditions involving an increase or a diminution in the functional activity of the thyroid or adrenal medulla. The increased resistance to insulin of diabetic patients suffering from Graves' disease or from septic infections which was predicted in our conception has been confirmed clinically.

The interrelationship of these three glands with reference to the glycogenic function of the liver, is summarized in a diagram published twelve years ago in my book.[1]

Since we are discussing the functional interrelationship of glands of internal secretion, it is appropriate to recall the fact that the conception of "internal secretions" was invented by Claude Bernard to describe the glycogenic function of the liver. In coining this term, "internal secretion," he wished to emphasize the autonomous glandular

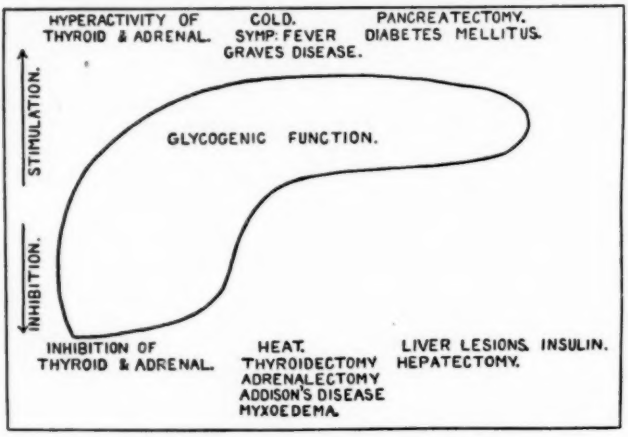

Fig. 1—Interrelation of thyroid, adrenal and pancreas in the glycogenic function of the liver.

nature of the glycogenic function of the liver which functions irrespective of the amount of carbohydrate ingested in the food, and even irrespective of the amount of glycogen present at any given moment in the liver, as opposed to the alternative interpretation of this function as a storage of an excess of carbohydrate in the food. The genius of Claude Bernard shines no more brightly than in this bold conception, which even today, in spite of the vast amount of work carried out on the subject, is not always fully understood.

We thus see that one of the ways, by which the functional activity of an endocrine gland may be stimulated, is as a compensatory response to a disturbance in the internal environment which may be created by the functional activity of another endocrine gland.

But in the compensatory response of an endocrine gland the typical effects of its hormone are masked partly or completely by those resulting from the disturbance of the internal environment which the compensatory response is intended to counteract. If this primary disturbance is sufficiently severe or prolonged, the endocrine gland providing the compensatory response may become extensively depleted of its load of hormone and the organism will then present a general condition, a syndrome, which will be erroneously interpreted as a dysfunction of the gland.

You will see the point of this conclusion, and of this lengthy introduction to our subject, when I describe to you the paradoxical condition induced by a continued excessive supply of the female sex hormone.[2] Prolonged estrinization produces in the animal slowly a syndrome which, though strikingly similar to that produced rapidly by hypophysectomy, is associated with an anterior pituitary gland showing the signs of intense functional activity. The syndrome is, as I just said, that of a dysfunction of the anterior pituitary. It closely resembles the syndrome of Simmonds' disease. When the estrogenic hormone is applied continuously over long periods it is found that every endocrine organ in the body is affected to a greater or smaller extent. In some of these organs it can be seen with the naked eye that they have undergone a change. In addition, the organism as a whole is profoundly affected. If young mice are used they are found to be stunted in growth, emaciated, in males the testes are so atrophied that they are difficult to find and if examined histologically spermatogenesis is absent. The thyroids are pale and small, the islets of Langerhans are greatly enlarged, there is an extensive and specific degeneration in the adrenal cortex, the thymus is completely atrophied and the lymph glands are smaller than normal. In short, the picture presented by these estrinized animals is very similar to that seen after hypophysectomy. But, and this is the paradox, if the pituitary is examined the anterior part is found to be deeply congested and greatly enlarged. The enlargement may be so irregular as to be called adenomatous. Histologically there is always a marked diminution in the number of the acidophile cells in the anterior part, and they may even be completely absent. In its extreme forms the condition may therefore be called a chromophobe adenoma.

Since Horning and I described this phenomenon it has been confirmed by a number of observers, who have interpreted it by saying that the estrogenic hormone inhibits the anterior pituitary. Their argument is that the anterior pituitary secretes a hormone which promotes growth. In estrinized animals growth is arrested. Hence, they argue the estrogenic hormone inhibits the anterior pituitary. But this conclusion has been drawn without examining the gland. Even a casual inspection, with the naked eye, of the pituitary after prolonged estrinization, showing a greatly enlarged and deeply congested anterior pituitary, should be sufficient to cast some doubt on such an interpretation.

The method of functional histology which reveals that the secreting cells have discharged their specific hormones, confirms the conclusion that the estrogenic hormone has stimulated the anterior pituitary to continued functional activity as a compensatory response to restore the disturbance in the internal environment produced by the effects of the continued excess of the female sex hormone.

The two important points in this argument are: (1) *the anterior pituitary is stimulated and not inhibited by the estrogenic hormone;* (2) *the anterior pituitary secretes a hormone antagonistic to the estrogenic hormone.*

The correctness of this conclusion can be verified by an experimentum crucis.[3] If the activity of the anterior pituitary is a compensatory response to estrinization, the hormone or hormones which the anterior pituitary secretes should be able to antagonize the effects of the estrogenic hormone. That is the case. If certain hormone preparations from the anterior pituitary are injected simultaneously with the application of the estrogenic hormone, many of the effects of the latter are abolished or greatly diminished: there is no arrest of growth, no emaciation, no atrophy of the gonads, no congestion, and only a slight enlargement of the anterior lobe, and the chromophile cells retain their secretion. Only the degenerative change in the adrenal cortex cannot be prevented by the pituitary extracts. It is probable, therefore, that the adrenal cortex responds directly to the estrogenic hormone, while the changes in growth and in the gonads are brought about through the intermediation of the pituitary.

I turn now to the effects of prolonged estrinization on the adrenal glands.[4] In these glands a specific degeneration, not previously described, develops in a sharply circumscribed area, namely the innermost zone of the cortex, the zona reticularis. It begins as an enlargement of isolated cells, which acquire a brownish color with small lipoid inclusions. As these cells enlarge, several of them coalesce to form isolated brown masses, and eventually these coalesce to form a brown ring surrounding the medulla and separating it from the cortex. These masses consist of a structureless network showing a few nuclei which is impregnated with a brown material having the solubility of lipoids. Such a process of degeneration represents a reaction the opposite to that of the hyperemia and hypertrophy seen in the pituitary. While the changes in the anterior pituitary indicate a secondary compensatory stimulation, those

in the adrenal cortex should be interpreted as a secondary compensatory inhibition. On the axiom of an endocrine interrelationship functioning to maintain the internal environment constant, such an inhibition as a secondary phenomenon to the excess of one hormone should be interpreted as a compensatory diminution of the secretion of a synergic hormone from the adrenal cortex.

This interpretation of a synergism between the ovary and the adrenal cortex is supported by several facts. There is, firstly, the close histogenetic relationship between the ovary and the adrenal cortex. There is, secondly, the fact that both male and female sex hormones have been demonstrated in the adrenal cortex. Thirdly, there are the results of removing the adrenal glands.[5] Mice survive the operation fairly well when it is carried out in two stages. About 50 per cent of the animals remain alive and well for many months even when there is no accessory cortical tissue visible to the naked eye such as small cortical adenomata. It was surprising to find that the mortality from adrenalectomy could be greatly diminished by estrinization if begun a few weeks before the operation, but not if started immediately after it. This suggests that the preliminary treatment with an excess of the estrogenic hormone had so altered the endocrine balance as to protect the organism against the loss of an adrenal cortical hormone. This again indicates a synergism between the functional activity of the ovary and the adrenal cortex. It was even more surprising to find that these adrenalectomized mice no longer reacted to an excessive supply of estrogenic hormone in the same way as intact animals. The striking changes in the pituitary are either less well-marked or absent. Other typical effects of estrinization, loss of weight, arrest of growth, atrophy of the testes and of the thymus, are also absent or greatly diminished, and sometimes the animals, instead of being small and emaciated, become abnormally large and fat. The thymus and the lymph nodes are then frequently enlarged and even malignant tumors of the thymus with metastases have developed. In adrenalectomized and estrinized mice, the mammae do not develop as fully under the influence of the estrogenic hormone, the testes do not undergo atrophy as they do in intact animals. Generally speaking, therefore, the *loss of an adrenal hormone* confers a similar protection against an excess of estrogenic hormone as an *additional supply of an anterior pituitary hormone*. This again shows that in relation to the estrogenic ovarian hormone the anterior

pituitary and the adrenal cortex oppose each other. That this adrenal hormone is secreted by the cortex, and not by the medulla, is shown by the fact that adrenalectomized mice in which even a very small cortical adenoma was present exhibited the same reaction to estrinization as intact mice.

In a paper published in January, 1939, we argued from these results that the adrenal cortex possesses hormonal functions synergic with those of the ovary and that this synergism extends even to the etiology of cancer of the mamma. A few months later, Woolley, Fekete and Little[6] published the remarkable results of an experiment begun long before our publication, which are a striking demonstration of this conception. They had ovariectomized mice immediately after birth. Six months later the uterus and the mammary glands of these animals showed the atrophy one expects to find in the absence of the ovaries. But if such mice were allowed to live for a year or more, both the uterus and the mammae were found to be fully developed and 40 per cent of the mice which belonged to an inbred strain with a high incidence of mammary cancer (50 per cent in virgin females) developed cancer of the mamma. Special care was taken to prove the complete absence of ovarian tissue in these mice. But there was a striking abnormality in these spayed mice: namely, a massive nodular hyperplasia of the adrenal cortex, which in three of the animals had progressed to malignant tumors of the cortex. In those experiments, then, the removal of one endocrine organ had brought about, after a sufficiently long interval, a compensatory stimulation of another endocrine organ with a synergistic function, "thereby simulating or replacing ovarian activity," to use the authors' own words.

As long as we consider these divers experimental results by themselves as isolated facts they remain curious and puzzling phenomena. But they form a coherent picture on the basis of the conclusion that the adrenal cortex secretes a hormone which acts as a synergist to the ovarian estrogenic hormone and in the last mentioned experiments of Woolley, Fekete and Little as a partial substitute. If we take the functional relationship between the ovary and the adrenal cortex as an example of two endocrine glands secreting synergistic hormones, we can express their relationship in general terms by saying that the *hyperfunction of one endocrine gland*, in this case the ovary, *induces in the gland secreting its synergist a hypofunction*, exemplified by the

brown degeneration of the cortex, while the *inhibition of one endocrine gland*, produced experimentally in this instance by removal of the ovaries, *induces in the gland secreting its synergist a hyperfunction*, exemplified by the nodular hyperplasia of the cortex. The two opposite reactions induced experimentally in the adrenal cortex–by ovariectomy on the one hand and by an excessive supply of the estrogenic ovarian hormone on the other–are both compensatory phenomena tending to correct two opposite disturbances in the endocrine balance in opposite directions.

In connection with the observation that after adrenalectomy the thymus fails to undergo atrophy under the influence of the estrogenic hormone, it is necessary to mention briefly the effects of adrenalectomy alone. It was found that in adrenalectomized animals the thymus persists or rather regenerates and the lymph nodes are enlarged. In view of the fact that our knowledge of the functions of the thymus and of the factors controlling this organ and the lymphoid system generally are very scanty, this demonstration that the thymus and the lymphoid system are under endocrine control is important. On looking through the literature I find that this effect of adrenalectomy has been observed 15 years ago here in New York, in a convincing series of experiments, by Marine and his collaborators.[7, 8] It is curious that the experimental demonstration of this surprising relationship has aroused so little interest either among physiologists, pathologists or clinicians. There are hardly any references to it in the text-books. But there is a definite pathological condition, status lymphaticus, in which the most obvious abnormality is a persistent thymus, associated with hypoplastic lesions in the adrenal gland. In a summary of the clinical, pathological and experimental evidence Marine[9] has shown that the condition produced experimentally is strikingly similar to that found as a disease in man, although the name given to the disease, "status lymphaticus" or "status thymo-lymphaticus," gives undue prominence to a symptom rather than to the underlying cause. But this is no reason why the existence of this syndrome, adrenocortical hypofunction with hyperplasia of the thymus, as a separate and definite clinical entity should be refused recognition, as has been done officially in England.

I pass on, now, to the changes in the adrenal medulla observed in animals subjected to prolonged estrinization. They are not nearly as striking as those seen in the cortex. The medulla exhibits a moderate

degree of active secretion, so that this part of the adrenal certainly does not show an inhibition. But the activity of the medulla is not sufficiently impressive to be in itself accepted as evidence of a secondary compensatory secretion of an antagonistic hormone similar to the process seen in the anterior pituitary. There is, however, other, indirect evidence to add support to such a conclusion. As already stated, adrenalectomized animals in which a small cortical adenoma has remained, react to estrinization at least as readily as intact animals. This seems surprising since the amount of cortical tissue present is often minute, less than a pin's head. But such animals do not contain any medullary cells. If the functional activity of the medulla can be assumed to counteract the estrogenic hormone, this high sensitivity to estrogenic hormones of animals completely devoid of medullary cells, but possessing a small amount of cortical tissue, can be accounted for. The study of the adrenal gland of various highly inbred strains of mice with a high and a low incidence of mammary cancer has brought to light facts which lend further support to this conclusion. There are inbred strains of mice which by their high incidence of spontaneous mammary cancer in females indicate a high susceptibility to mammary cancer and to the action of the estrogenic hormone. Thus, in the males of high cancer strains this hormone induces mammary cancer more rapidly and in much greater number than in the males of low cancer strains. Now in two such high cancer strains which have been examined, the adrenal medulla undergoes spontaneously a process of brown degeneration which begins at an early stage and is progressive, so that eventually it destroys the greater part of the medulla.[4] It occurs in practically every animal, both male and female, of the two high cancer strains examined, and in the females it is already present before cancer develops spontaneously. In a considerable number of other strains which have a very low incidence or do not develop cancer at all, this process of brown degeneration either does not appear at all in the medulla or if it does develop, it does so late in life and is then very circumscribed in its extent.[10] This spontaneous disease of the adrenal medulla, which diminishes the functional activity of the medulla, is thus associated with a high susceptibility to the effects of the estrogenic hormone and also with a greater susceptibility to the general effects of this hormone. The work of H. S. N. Greene[11] on inbred rabbits has disclosed a very similar condition—the spontaneous development of pathological changes in the adrenals

and in the pituitary in association with the spontaneous development of mammary cancer. This association–increased susceptibility to the ovarian hormone and diminished functional activity of the adrenal medulla–suggests again an antagonism between the ovarian and the medullary hormones. The two parts of the adrenal gland secrete, therefore, two hormones which in their relation to the ovarian estrogenic hormone oppose each other. It is interesting to note that the same conclusion of a functional antagonism between the two parts of the adrenal gland has been arrived at by Marine as the result of his studies on the thyroid gland and its relationship to the rest of the endocrine system.

The functional relationship of the ovarian estrogenic hormone to the anterior pituitary and the adrenal glands is therefore a complex one. Like the relationship between the thyroid, the adrenal medulla and the islets mentioned at the outset of this lecture, it arranges itself into a pattern of an endocrine balance between synergists and antagonists. The anterior pituitary and the adrenal medulla secrete hormones antagonistic to the estrogens, the adrenal cortex a synergistic one. A disturbance of this balance produced by the excessive functional activity of the ovarian hormone leads to a secondary compensatory inhibition of its synergist, the adrenal cortex, and a secondary compensatory stimulation of its antagonists–the anterior pituitary and the adrenal medulla. These responses tend to restore the balance. Huse, in a book with the piquant title, "The Illiteracy of the Literate," criticizes loose argumentation based on abstract terms. He says: "Unfamiliar terms are understood by translation into the familiar; abstractions by translation into concrete terms. . . . We have no guide except our own experience." I have therefore translated this abstract relationship of a balance into concrete terms. I have attempted to represent this by devising the following diagram which represents literally an endocrine balance. As this diagram, Figure 2, was drawn up originally with the special view of its bearing on cancer of the mamma, the movements of the pointer indicate the changes taking place in the mamma. But the mamma could be replaced by some other organ, such as the testis, or by some general condition of the organism, such as skeletal growth, or obesity and emaciation.

The endocrine organs concerned in this balance have been restricted to the anterior pituitary and the two parts of the adrenal, because the

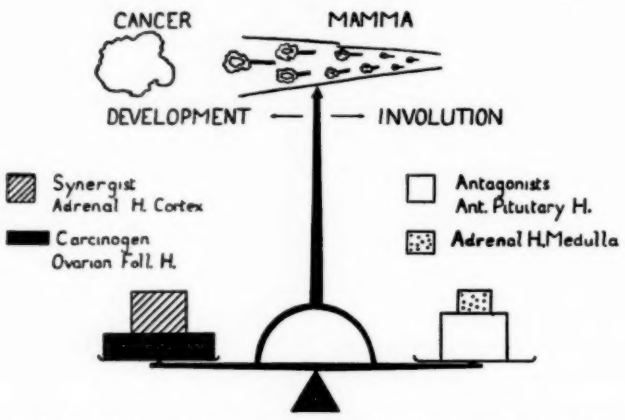

Fig. 2—Diagrammatic representation of an endocrine balance.

functional relationship between these three glands and the estrogenic hormone is almost certainly a direct one. The changes in the testis, the thyroid and parathyroids and the islets are probably secondary to those in the anterior pituitary, so that the anterior pituitary provides a relay mechanism by which the effects of one hormone may be transmitted to other endocrine glands. This diagrammatic representation affords an interpretation of the perplexing complexity of changes in the whole endocrine system which appear as the result of a prolonged excessive supply of the ovarian estrogenic hormone. It provides a working hypothesis the correctness of which can be tested by the results of experiments. The partial or complete inhibition of the effects of prolonged estrinization by adrenalectomy on the one hand, by a continued supply of an anterior pituitary hormone on the other, the partial functional replacement of the secretory activity of the ovary by the adrenal cortex, as revealed by the work of Little and his co-workers, the association of a spontaneous degenerative process in the adrenal medulla with an increased susceptibility to the estrogenic hormone, can all be read off from this diagram.

An excessive supply of the estrogenic hormone of the ovary depresses the left scale. In order to bring back the balance to its zero point the organism reacts to this excessive supply of the estrogenic hormone by an inhibition of the adrenal cortex, which secretes a synergistic hormone. Such an inhibition is represented by the brown de-

generation in the adrenal cortex. There is also a compensatory stimulation of the glands secreting the antagonistic hormones, the hyperemia and hypertrophy of the anterior pituitary with disappearance of the acidophile secretion, and the slight stimulation of the adrenal medulla. The difference in the relative sizes of the weights representing these two glands in the diagram is intended to indicate differences in the degree of their relative antagonistic action as judged from their compensatory stimulation. Experimentally the endocrine balance can be restored either by a continued administration of an anterior pituitary hormone, represented histochemically by the acidophile secretion, or by the removal of the adrenals. The synergistic effect of the adrenal cortex being stronger than the antagonistic effect of the medulla, the net result of a complete removal of the adrenal is a weakening of the synergistic cortical effect. A disturbance of the endocrine balance in the same direction as that induced by an excessive supply of the ovarian hormone can be induced by a diminution of the functional activity of its antagonists. This is represented by the spontaneous brown degeneration of the medulla in some inbred strains of mice with a high susceptibility to mammary cancer. In theory a primary disease of the anterior pituitary which specifically diminishes or inhibits the secretion of the acidophile cells should also be able to bring about a depression of the left scale with—amongst other things—an increased susceptibility to mammary cancer.

The opposite movement of the endocrine balance, an upward movement of the left scale, can be brought about by a removal either of the ovaries or of the adrenals. As just stated, adrenalectomy owing to the preponderance of the synergistic cortical effect has as a net result the removal of this synergistic cortical hormone. If the adrenals are removed there is an attempt by the organism to restore the balance by an inhibition of the antagonistic function of the anterior pituitary gland, which now does not respond as readily to the effects of the estrogenic hormone as in the intact animal. Experimentally the balance can be restored by an additional supply of the estrogenic hormone, and we have seen that this protects the organism against the loss of the adrenal cortex. The work of Woolley, Fekete and Little, on the effects of ovariectomy, which I have mentioned, also conforms to it. In their ovariectomized mice the endocrine balance was restored spontaneously by a nodular hypertrophy of the cortex in accordance with

the position of the adrenal cortex in the diagram. The point of general importance which emerges from these considerations is that a swing of the pointer to the left or to the right can be brought about in a variety of ways, or in terms of pathology, this means that a given syndrome may be due not to *one* particular change in *one* particular endocrine gland, but to *different* changes in several *different* endocrine glands.

As already stated, the significance of the changes in the thyroid, parathyroid and the islets requires further investigation. There is a marked enlargement of the islets and of the parathyroids, while the thyroid is small, pale and histologically presents a resting condition. It is possible that some of these changes are induced, not directly in response to the excessive supply of the estrogenic hormone, but, like the atrophy of the testis, indirectly as the result of the secondary changes induced in the pituitary. But it is clear that directly or indirectly the action of the estrogenic hormone embraces a wider range of endocrine activities than that of any other single hormone.

In this respect it stands in striking contrast to the male sex hormone, testosterone, in spite of the close chemical similarity of the two hormones. It is evident from their chemical similarity that both are formed from the same mother substance and it is probable that these two substances represent two stages in the same chemical process, the female hormone being probably the end product, while the male hormone represents an intermediate stage. This accounts for the otherwise remarkable fact that both these hormones are present in the male and in the female, and that, for instance, large amounts of the female sex hormone have been isolated from the testes of stallions. To those who are romantically inclined it may appear as a disappointment that the tragedies of star-kissed lovers, of Romeo and Juliet, of Abelard and Heloise, and of thousands of other mute inglorious ones were brought about by an additional CH_3 group and the absence of a double linkage. As Greta Garbo says in Ninotchka, love is simply a question of chemistry. Since both sex hormones are present in the male and in the female, what we call masculinity and femininity results not from the presence of one sex hormone and the absence of the other but from a different hormonal balance between the two.

The most important difference between the two is that the female sex hormone is much more powerful than the male one. An excessive

supply of the male sex hormone—even in large doses—does not produce any of the striking effects on the pituitary and on the adrenal cortex which can be induced by very small doses of the female hormone. The anterior pituitary is *not* enlarged or congested and there is *no* brown degeneration in the adrenal cortex after the prolonged administration of testosterone. There is, however, evidence that some functional relationship between the male sex hormone and the anterior pituitary and adrenal glands exists. This relationship manifests itself when the testes are removed. In the anterior pituitary some of the cells undergo a degenerative change which disappears again when testosterone is supplied experimentally. A striking change is produced by castration also in the adrenal medulla.[12] The peripheral cells of the medulla lose their adrenalin content partly or completely, so that the functional part of the medulla, i.e., the number of medullary cells containing adrenalin, is greatly diminished indicating an inhibition of the functional activity of the medulla. The medullary cells which have lost their adrenalin content lose thereby their characteristic morphological appearance as medullary cells, especially when they are examined by the routine histological methods. They have thus been mistaken for cortical cells. There is also a change in the innermost zone of the cortex, the zona reticularis, the cells of which enlarge and assume a morphological appearance very similar to the peripheral cells of the medulla which have lost their load of adrenalin. The appearance is thus created of the formation of a new zone of the cortex. But this new zone is not an addition to the gland, for the gland shows no corresponding increase in size: this zone has been formed mainly at the expense of the medulla, which is diminished in size and which no longer shows a sharp separation from the cortex but has an irregular outline with islets of adrenalin containing cells lying within this new zone separated from the central medullary mass. The appearance of the adrenal gland of a male mouse after castration is thus similar to that seen in young female mice, but rarely in old females. The apparent new zone is, in fact, the so-called X zone about which so much has been written in the literature to the effect that it is an independent zone. This view is untenable both on mechanical and on experimental grounds.[4] It is due to the use of histological methods not adequate for investigations of this kind. When testosterone is administered to castrated male mice, the broad zone, i.e., the X zone, rapidly disappears again without any corresponding alteration in the

size of the gland. It disappears because the peripheral cells of the medulla, which had lost their load of adrenalin, become filled again with adrenalin granules and because the innermost cells of the cortex shrink. The result is that the central medullary mass of adrenalin-containing cells increases in volume and presents again a regular outline sharply differentiated from the cortex. The estrogenic hormone shows a significant difference from the male sex hormone in not being capable of producing this effect. The diminution in the volume of adrenalin-containing medullary cells when the male hormone is absent is clearly an inhibition; the increase in volume by replacing the missing testosterone is equally clearly a stimulation. This effect corresponds to the relationship given in the table shown at the beginning as existing between glands secreting antagonistic hormones. The swelling of the innermost cells of the cortex after castration indicates a stimulation, in agreement with the known function of the cortex of forming both male and female sex hormones. The cortex is thus a synergist to the endocrine functions of both the male and the female gonads. It reacts accordingly by increased functional activity when the gonads are removed, and by inhibition when the male or the female sex hormone is administered.

The adrenal changes following removal of the testes and their disappearance by the administration of testosterone are the most striking features in the relationship of the male sex hormone to the other endocrine glands which have been found so far in addition to the well-known castration effect on the pituitary. It may be recalled for purposes of comparison that the outstanding effect of the estrogenic hormone on the adrenal is also an inhibition of the cortex and a stimulation of the medulla. But with the ovarian hormone these effects manifest themselves differently, and are more pronounced in the cortex, while it has only a weak stimulating effect on the medulla. Perhaps that quality which we call "virility," as distinct from virilism, is a manifestation of the strong stimulating effect of the male sex hormone on the adrenal medulla. It is not fanciful to see a connection between the wide range of endocrine activities capable of being influenced directly or indirectly by the female sex hormone and that quality of femininity: "The infinite variety which time cannot wither nor custom stale." There is abundant evidence that the functional activity of some endocrine organs affects the mind and can, in turn, be affected by the mind. The shivering of fear, of cold and of a high fever have the same origin in the secretory

activity of the adrenal medulla. The difference between the nervous, restless, excitable hyperthyroid and the slow, dull, apathetic hypothyroid is another example. This difference between the male and the female sex hormones may also be correlated with the greater frequency in women of psychoses in disturbances of ovarian function such as menstruation, the puerperium, lactation and the menopause.

The hormonal relationship between the ovary, the anterior pituitary and the two parts of the adrenal gland conform to the same general pattern which exists between the adrenal, the thyroid and the pancreatic islets and which we represented in Table I. It indicates that a functional activity of an endocrine gland can be elicited as a compensatory phenomenon either by the hyperfunction of its antagonist or by the hypofunction of its synergist.

This interrelationship affords an explanation of the position of the pituitary gland in the endocrine system. At present it is generally believed that this gland *dominates* the endocrine system. It has been described metaphorically as "the leader of the endocrine orchestra." This conception is, as far as I know, based mainly on the fact that removal of the pituitary is followed by atrophic or degenerative changes in almost all the other endocrine glands and that different extracts of the pituitary have the power to repair these degenerative changes. But we have seen that the excessive functional activity of another endocrine gland, the ovary, can produce a syndrome very similar to that following a hypofunction or removal of the pituitary. It is clear, therefore, that the pituitary is by no means the leader of the endocrine orchestra. The evidence presented shows that the pituitary is deeply influenced by the female member of the endocrine orchestra. The relationship between the ovary and the pituitary is, in fact, a reciprocal one, the two glands secreting hormones which antagonize each other. There is evidence of a similar reciprocal relationship between the pituitary and some other endocrine glands. The pituitary changes resulting from the activity of other endocrine glands have been studied in greatest detail in their relationship to the male and female gonads and to the thyroid gland. From the survey of Sevringhaus on the anterior pituitary, the three conditions, castration, pregnancy and thyroidectomy, produce the same pituitary changes, a hypertrophy of the gland with a diminution of the acidophile cells and an increase in the basophiles. The administration of the thyroid hormone to a thyroidectomized

animal restores the number of acidophiles. From a study of the interrelationship of the thyroid and the anterior pituitary Marine and his collaborators[13] come to the conclusion that the anterior pituitary is as much under the influence of the thyroid hormone as the thyroid is influenced by the anterior pituitary hormone. There is evidence that the anterior pituitary is also affected by the functional activity of the adrenal cortex. If we speak of the pituitary hormones as gonadotropic, thyrotropic and adrenalotropic, we can equally well speak of the hormone of the gonads, thyroid and adrenals as pituitarytropic. The term "tropic" as applied to the pituitary hormones is a vague one, and it is very properly vague. It indicates merely the existence of an interrelationship, and should not be taken as predicating that this relationship is a direct and one-sided one. As a working hypothesis the so-called "tropic" effect of anterior pituitary hormones on some other endocrine glands may be regarded as the manifestation of the functional relationship existing between endocrine glands secreting antagonists as shown in Table I.

We thus get a glimpse of the position held by the anterior pituitary in the endocrine system; it is a compensatory mechanism which comes into play when the primary functional activity of another endocrine gland disturbs the endocrine balance. That is its physiological response. Pathological conditions result when the capacity of this compensatory mechanism is strained by the effect on the anterior pituitary of a prolonged, primary change in another endocrine gland. The pituitary then undergoes more profound changes as a secondary effect. By virtue of the relationship of the pituitary to the other endocrine glands, the altered pituitary acting as a kind of relay induces in them, as a tertiary effect, functional activity or functional inhibition, thus producing a multiglandular endocrine disturbance. If this conception be correct, one would expect to find diseases of *one* endocrine gland, especially diseases which are slow to develop, to be associated with pathological changes in some other endocrine glands and especially in the anterior pituitary. Furthermore, there is the possibility that the gland most obviously affected may not be the primary cause of the disease, even though it is at present generally regarded as such. There is already a group of endocrine disorders of obscure origin and classed together as multiglandular diseases. But, until recently, most endocrine diseases have been generally identified with a diseased condition of one single endocrine gland.

Exophthalmic goiter is an example par excellence. It has been generally identified with hyperthyroidism. Hyperthyroidism is one feature of its syndrome. But it has been difficult to induce exophthalmos experimentally by giving thyroxin. Schockaert[14] and Loeb and his coworkers[15] have made the interesting discovery that exophthalmos can be induced experimentally in young animals by the injection of anterior pituitary extract. Subsequently Marine and his colleagues found that the experimental production of exophthalmos is facilitated by subtotal thyroidectomy, and furthermore that the exophthalmos thus produced can be made to disappear by the administration of thyroxin. As the result of his experimental and pathological observations Marine[16] has arrived at the conclusion that the presence of exophthalmos in Graves' disease is dependent on two factors: thyroid insufficiency and pituitary hyperactivity. He suggests that the primary endocrine disturbance leading to the syndrome of Graves' disease lies outside the thyroid, probably in the testis or in the adrenal cortex, where pathological changes are frequently found in Graves' disease. This primary endocrine disturbance induces a hyperactivity of the thyroid as a compensatory response.

Another example is Cushing's syndrome which Cushing himself associated with a basophile adenoma of the pituitary. But the same syndrome has also been found in cases where the anterior pituitary was normal or only slightly abnormal, but where there was a hyperplasia of the adrenal cortex, or an arrhenoblastoma of the ovary and even in cases of malignant tumor of the thymus. This is a demonstration of the important fact, emphasized in another part of this lecture, that the same syndrome can be induced by different combinations of endocrine disturbances. Another example of this remarkable fact is supplied by the paradox mentioned at the outset of this lecture. The syndrome, produced experimentally by removal of the pituitary, or known clinically as Simmonds' disease, where it is associated with a degenerative disease of the anterior pituitary, has been produced by us experimentally by an excessive supply of an ovarian hormone. In the last mentioned condition, the syndrome is associated with an enlarged and deeply congested pituitary, which has been exhausted by prolonged functional activity and may present the condition of a chromophobe adenoma. This does not imply that the three conditions are identical, either etiologically or symptomatically. In Simmonds' disease, as after hypophy-

sectomy, the mamma is atrophic. The difference in the condition, induced by the estrogenic hormone, is the presence, even in males, of a well developed mamma or even of mammary cancer. The point I wish to make again is that a characteristic group of symptoms can be induced from different endocrine angles. It has been argued that the doses of estrogenic hormones necessary to induce pathological changes in the pituitary and the adrenals are so large, that they can have no bearing on the etiology of similar conditions in the human subject. But Bagg[17] has succeeded in producing similar lesions in the pituitary and the adrenals by subjecting the ovaries of rats to the functional strain of rapidly repeated breeding. These observations of Bagg conform to the work of Greene[11] mentioned previously in showing that the ovary can under abnormal conditions secrete sufficient hormone to induce pathological changes in other endocrine organs.

The part played by the islets in the etiology of diabetes mellitus is, I believe, still obscure in the sense that pathological lesions of sufficient severity to account for the condition are not always present. Perhaps here, too, some other glandular lesion is involved. Obesity is still another example of a syndrome which can be reached from divers endocrine angles. The psysiology of adipose tissue is a subject which has received little attention, as Gideon Wells points out in a recent review of the literature entitled: "Adipose Tissue: A Neglected Subject."[18] But both as a physiological and as a pathological problem it has hidden scientific charms. The formation of fat in the organism is dependent on a glandular structure, dispersed throughout the body in small cellular aggregations and subject to endocrine influences, as I pointed out 20 years ago. Pathological obesity can result from a primary dysfunction either of the gonads or of the anterior pituitary or of the thyroid, and, according to some authors, also of the pancreatic islets.

It is perhaps appropriate to mention in this connection that the possibility of inducing profound changes in the pituitary and the other endocrine organs as the result of the prolonged administration of estrogenic hormones should be borne in mind in the therapeutic administration of this ovarian hormone over prolonged periods. This is a danger which is more likely to be incurred than the more remote, although the more serious one, of inducing cancer of the mamma. Of this latter possibility I have already expressed my opinion in other papers. I need not refer to it again, therefore, beyond saying that the therapeutic

value of the estrogenic hormones is so high that their use should not be discredited by either overrating or underrating the dangers resulting from their use. In my opinion there is no danger in the therapeutic administration of an estrogenic preparation over short periods of time of several months, in doses just sufficient to produce the desired therapeutic effects. When this hormone has to be given over prolonged periods of a year or several years, the danger of inducing endocrine changes can be avoided by giving the estrogens in therapeutic doses and discontinuously in courses lasting for three or four months, interrupted by periods of rest. The administration of estrogenic hormones by the inoculation of pellets is, I believe, dangerous and inadvisable.

Summary

I have tried to lay before you a conception of the endocrine glands as forming a single system of great complexity and delicacy, in which the functional activity of each individual gland is regulated partly by that of its antagonists and its synergists. It thus enables a highly differentiated organism to adapt itself effectively to changes in the external and internal environment. The test of such physiological conception is its applicability to diseases of the endocrines. As our knowledge of the pathology of these conditions advances it is becoming increasingly evident that in many of them more than one endocrine organ is involved and that their etiology is much more complex than simply the identification of such a disease with a pathological condition in one single gland. An ideal pathological examination of a case of an endocrine disease should, therefore, involve the examination of every endocrine organ. Such material if collected in an endocrine register would materially advance our knowledge of the etiology of endocrine diseases by making it possible to correlate these conditions with experimental observations. And I may add that there are still a number of conditions not yet recognized as of endocrine origin, in which profound changes can be seen in such organs as the thyroid or the adrenal. I speak from personal experience when many years ago I collected material from autopsies of cases which had died in hyperpyrexia, the microbic origin of which had not been established.

From a confused heap of pieces of a picture puzzle we have taken some and tried to put them together without any preconceived notions. The picture which I have described to you has resulted. It is an attempt

at a functional integration of a group of endocrine organs.

All I claim for the views I have expressed tonight is that they are a working hypothesis based on experimental observations. A working hypothesis is one which stimulates work with the object of either confirming it, or of refuting it by replacing it by a better one. If I have attained this object I shall feel that I have fulfilled the obligation which I undertook when I accepted the invitation with which you have honored me.

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THE BLOOD PLASMA FOR GREAT BRITAIN PROJECT*

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It seems appropriate to report to this Committee on the present status of the Blood Plasma for Great Britain Project for which the Academy is indirectly responsible, as it was initiated by one of the Academy's many protégés, the Blood Transfusion Betterment Association. The development of this project is an example of how the Academy, largely through its Committee on Public Health Relations, has not only a local and national, but even an international influence in the field of public health.

Because we had been informed from reliable, authoritative sources that the Allies, particularly the British, were in urgent need of appropriate blood substitutes for the emergency treatment of shock and hemorrhage, on June 12, 1940, a special joint meeting of the Board of Trustees and the Board of Medical Control of the Blood Transfusion Betterment Association was called at the Academy to discuss the question of supplying the Allies with blood plasma, which does not require blood grouping, as the most effective product for their needs. To this meeting were invited: Herbert B. Wilcox, the Director of the Academy, Alexis Carrel and several other scientists who have been working especially on blood preservation and blood substitutes, Captain Douglas B. Kendrick, Jr., Medical Corps, representing the Surgeon General of the Army, and representatives of the various larger commercial houses who are preparing and marketing blood serum or plasma. It was decided that we should act at once and this meeting was immediately followed by a meeting of the Board of Trustees where it was voted that the Association sponsor the production and shipment of blood plasma to the Allies provided the American Red Cross was willing to coöperate. The Board of Trustees voted an appropriation of $15,000 from their treasury toward financing this project. At a subsequent meet-

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ing on August 1, an additional appropriation of $5,000 was voted, to be reserved for research.

On June 18, Mr. John F. Bush, President of the Board of Trustees of the Blood Transfusion Betterment Association, Mr. Tracy S. Voorhees, a member of the Board, and I went to Washington and had a lengthy interview with Mr. Norman H. Davis, Chairman of the American Red Cross, his chief aide, Mr. DeWitt C. Smith, Director of Domestic Operations, and William DeKleine, Medical Adviser. We presented our tentative plan for the organization of the blood plasma project. They were much interested and very sympathetic, especially in view of the fact that we pointed out to them that, in addition to this work for the Allies who, of course, since that time have come to mean the British, the development of this project would eventually be of great use for our own national defense program in supplying plasma to our armed services. They, however, at that meeting were rather noncommittal as to what assistance they would give us.

Later the same day we had an interview with Colonel Charles C. Hillman, Medical Corps, of the Office of the Surgeon General of the Army, who was very encouraging and who referred us to the special Subcommittee on Blood Substitutes of the National Research Council, of which Cyrus C. Sturgis, Professor of Medicine of the Medical Department of the University of Michigan, is Chairman. The Army was being guided on this question by the advice of this Subcommittee. Contact was promptly established with Sturgis who endorsed our plan wholeheartedly. After considerable correspondence and telephonic conversations to and fro, on July 26, Mr. Bush, Mr. Voorhees and John Scudder, whose enthusiasm for the project was a great stimulus to us and who was subsequently appointed Assistant to our Board of Medical Control, again had a conference in Washington with Mr. Norman H. Davis, Mr. Ernest J. Swift, one of the Vice-Chairmen, and Mr. DeWitt C. Smith. The result of this conference was that the Red Cross agreed to coöperate with us to the extent of advancing us $25,000, with an eventual additional grant of $5,000, and of conducting the publicity campaign to obtain for us the necessary volunteer donors. The Blood Transfusion Betterment Association was to direct the procuring of blood and the production of the plasma. The plasma was then to be delivered to the Red Cross in New York City which would attend to its shipment abroad.

We commenced immediately with six hospitals: Presbyterian, Mount Sinai, New York Post-Graduate, New York, Long Island College and Memorial; and in the beginning of October two other hospitals, Lenox Hill and Hospital for Joint Diseases, were added. Four additional hospitals have now been approved by the Board of Medical Control and will function if required: French, Ruptured and Crippled, Brooklyn Hospital and Jewish Hospital, Brooklyn. Most of these hospitals have installed the major equipment needed, such as iceboxes, incubators, centrifuges and electric pumps. In exceptional instances we have furnished a centrifuge or a centrifuge head and cups. In all cases we have supplied transfusion sets, bottles, stoppers, caps, labels, record books, record cards and release forms. Of course, the service of all the doctors, nurses and technicians is donated. We pay the hospital $1.50 per liter of the finished product for out-of-pocket laboratory expenses, etc.

The Academy, which has always been most generous in giving us meeting rooms, presented us with commodious quarters for a central managing, recording and donor distributing office and an elaborate telephone and record system was at once established in these quarters. Mr. Morris M. Davidson volunteered his services and was appointed Director of what we have called the Blood Plasma Division of the Association. A staff of twenty-two paid secretaries, clerks and telephone operators was eventually employed. Pettit & Reed offered us the services of a special refrigeration truck for collection of the product from the various hospitals and the facilities of their refrigeration warehouse for storage until shipment by the Red Cross. The call for volunteer donors by the Red Cross was made through the press, over the radio and by the wide distribution of descriptive posters and pamphlets. It apparently had a very strong popular appeal, judging by the immediate enthusiastic response from every stratum of society. The first appointments for donors were made at The Presbyterian Hospital on August 15. Twenty-two donors were sent and twenty were accepted. The following day six donors were handled by The Mount Sinai Hospital. Since that time there has been an ever-increasing stream and, up to and including October 31, 9,556 appointments have been made—1,044 in August, 3,822 in September and 4,690 in October (Table I).

The actual number sent to hospitals was 8,132. Of these 1,171 did not appear; 6,961 actually arrived at the hospitals. To this number 404 were added by the hospitals themselves. Of this total of 7,365, 381, or

TABLE I

ANALYSIS OF APPOINTMENTS FOR DONORS BY HOSPITAL AND MONTH

Hospital	August	September	October	Totals
Presbyterian	762	1203	1012	2977
Mount Sinai	199	577	901	1677
New York Post-Graduate	12	555	791	1358
New York	11	469	552	1032
Long Island College	60	464	422	946
Memorial	...	391	363	754
Lenox Hill	...	134	264	398
Joint Diseases	...	29	385	414
Totals	1044	3822	4690	9556

TABLE II

ANALYSIS OF DONORS BY HOSPITAL AND EVENT

Hospital	Donors Sent	Donors Lapsed	Donors Arrived	Donors Added by Hospital	Donors Rejected	Donors' Bloods Taken	Donors' Bloods Discarded
Presbyterian	2625	371	2254	132	120	2266	31
Mount Sinai	1415	203	1212	75	28	1259	5
New York Post-Graduate	1093	177	916	73	49	940	6
New York	956	102	854	14	56	812	12
Long Island College	759	144	615	60	28	647	14
Memorial	591	75	516	30	44	502	2
Lenox Hill	311	58	253	9	19	243	3
Joint Diseases	382	41	341	11	37	515	2
Totals	8132	1171	6961	404	381	6984	75

5.17 per cent, were rejected because of under- or over-age, general physical ineligibility, poor veins, low blood pressure, low hemoglobin percentage, history of communicable diseases, and acute upper respiratory infection or other pathology. The blood was actually taken from the remaining 6,984 donors. The blood from 75 donors, or 1.07 per

TABLE III

ANALYSIS OF WEEKLY QUOTAS OF DONORS FOR EACH HOSPITAL

Hospital	Donors
Presbyterian	250
Mount Sinai	240
New York Post-Graduate	180
New York	150
Long Island College	100
Memorial	85
Lenox Hill	72
Joint Diseases	100
Total	1177

TABLE IV

ANALYSIS OF PLASMA SALINE SOLUTION RELEASES BY HOSPITAL, MONTH AND QUANTITY

Hospital	Liters				
	August	September	October	November 1	Totals
Presbyterian	21	156	222	...	399
Mount Sinai	...	24	162	54	240
New York Post-Graduate	...	...	18	36	54
New York	...	...	42	60	102
Long Island College	...	...	90	23	113
Memorial	...	...	42	...	42
Totals	21	180	576	173	950

cent, was discarded because of positive or suspicious serology. The statistics from the various hospitals through October 31 are shown in Table II.

The eight coöperating hospitals are now prepared to handle 1,177 donors each week. The weekly quotas are shown in Table III.

The four additional hospitals, previously referred to, are each prepared to take 75 donors weekly, or an additional total of 300.

TABLE V

ANALYSIS BY HOSPITAL AND QUANTITY OF PLASMA SALINE SOLUTION AWAITING RELEASE IN WAREHOUSE

Hospital	Liters
Presbyterian	156
Mount Sinai	168
New York Post-Graduate	174
New York	90
Long Island College	102
Memorial	66
Lenox Hill	24
Joint Diseases	30
Total	810

Up to and including November 1, 1940, 950 liters of plasma saline solution have been released to the Red Cross as sterile and ready for shipment from the six hospitals originally coöperating (Table IV).

The latest report that we have on November 1, is that 747 liters of this solution have already been shipped abroad. In addition to this amount released for shipment through November 1, there were 810 liters of the solution at Pettit & Reed's waiting for the very rigid two weeks' culture quarantine that we have instituted and that is being controlled by our Bacteriological Consultant, Frank L. Meleney of The Presbyterian Hospital, who has very graciously placed his laboratory at our disposal for this purpose. This material comes from the eight coöperating hospitals as shown in Table V.

Further, there were about 700 liters of pooled plasma, equivalent to 1,400 liters of the final product, distributed in the iceboxes of the eight coöperating hospitals awaiting local culture reports before being added to the saline solution and sent to the central warehouse. Up to date, there have been 30 liters, or 3.15 per cent, of the solution lost because of contamination as checked by our central laboratory. This contamination was mostly in the early batches. Only one carton of 6 liters has been discarded in the last three weeks of October. Four

hospitals have reported losses due to contamination found in the hospital —the total amount of these losses being approximately 20 liters of plasma, or what would have made 40 liters of the solution.

As yet we have had no reports from London as to the real results from the use of the plasma but we have had a letter, under date of August 27, from Sir Edward Mellanby, Secretary of the Medical Research Council of Great Britain, telling us that the first batch shipped had arrived in good condition, had been cultured, found to be sterile and would be placed at the disposal of the Royal Air Force. We have also had a letter, dated October 8, from A. N. Drury, Chairman of the Committee on Traumatic Shock and Blood Transfusion of the Medical Research Council of Great Britain, stating that 7 cartons, or 42 liters, of the plasma saline solution had arrived safely and was proving very useful. We further received a second letter from Sir Edward Mellanby, dated October 25, urging us to continue sending the plasma at least until the end of January, 1941, and stating that he felt that by the time this shipment arrived in the latter part of February, the production of plasma in Great Britain would be on a sound basis and sufficient to take care of their needs.

On October 3, Mr. Bush, Mr. Voorhees and I again went to Washington to report to Mr. Davis and his advisers. They seemed quite pleased with what we had accomplished and, though they gave us no definite promise, indicated that we could count on continued financial support; for even if Great Britain had no further need for our product—which question was to be investigated—they felt that we had the organization for developing the best method of mass production and for settling most of the doubtful points about blood substitutes.

When we began this work we were led to believe that it would be relatively simple. We received the impression that preparing plasma would not be much more difficult than mixing a cocktail, but we soon learned, much to our distress, that such was not the case. When we began mass production of plasma for shipment abroad, to be used after a relatively long period had elapsed, we found that it was a vastly different proposition than the production of small quantities of plasma in a hospital for prompt use on the premises.

Unexpectedly, innumerable problems came up—some of which we have solved, but not all, as yet. Let me enumerate some of the more important of them:

First of all, which is the better blood substitute and which gives the least reaction—plasma or serum? For the time being we have decided on plasma.

Should we produce liquid or dried plasma? We settled on liquid plasma for the present as the equipment now in use for drying plasma was expensive, not entirely satisfactory and would take too long to install—and the time element was vital.

Should the blood be collected by an open or closed method? We have settled on the closed procedure.

How should the closed procedure be instituted? What type of bottle should be used—dumbbell, square straight-sided, or cylindrical? Should the neck be narrow or wide, straight or with sloping shoulders? What is the best size for the bottle? Should a double-holed, glass-tubed rubber cork or some form of vaccine stopper with a special double needle be used? Should vacuum, suction, or just the venous pressure be utilized in drawing the blood? If suction, what type? How should the blood be mixed with the sodium citrate solution? How should these bottles be corked or capped after filling? What is the best way of drawing off the supernatant plasma into the pool bottles? These questions are all being investigated at the moment. Some have been more or less settled, while some are still sub judice.

What should be the age limits, the minimum blood pressure, and the minimum hemoglobin percentage for the volunteer donors? Over 21 and under 60 years, 110 systolic, and 80 per cent, respectively, were our answers.

Should the blood be taken only from fasting donors to avoid turbidity of the plasma from fat globules? This was especially important in view of the fact that the British Medical Research Council had given instructions to their medical officers to discard turbid serum or plasma as turbidity probably indicated contamination. We preferred not to have the donors fast as they might faint more easily at the blood letting and as it was difficult from an administrative standpoint to get volunteer donors to abstain from eating. After explaining the situation by cable to the heads of the British Medical Research Council, they wired back that they would waive their objections in this respect for our product.

Should Negro blood be utilized? This was answered in the affirmative but with the proviso that the plasma therefrom should be specially labelled as to its origin.

What serological test for syphilis should be used? Any recognized test was considered acceptable.

Should blood with a plus-minus luetic test be used? It was agreed that blood with even the slightest suspicion of a positive serology should be discarded.

Should the blood of the donors be grouped? Although blood grouping is not necessary as regards the pooled plasma, it was felt that, nevertheless, the donors blood should be grouped for the donors' information as a slight reward for their donation. The Red Cross now furnishes every donor with a card stating that he or she has given his blood for this plasma project and on the card appears a notation of the donor's blood group.

Is sedimentation or centrifugation the better method of separating the plasma from the blood cells, from the standpoints of yield, sterility, speed and economy? Both methods are now being used in the different hospitals and the question is being carefully studied, but as yet no definite decision has been reached.

How much and what strength sodium citrate solution should be used? We have settled on 50 cc. of a 5 per cent solution for every 500 cc. of blood.

What strength merthiolate solution should be used as a bacteriostatic and bacteriocide? We are now using 1 to 10,000, but there is some question as to its efficacy and an increase of strength is under consideration.

What is the best type and size of pool bottle? We selected a two-liter Baxter bottle.

How much normal saline solution should be added to the plasma to keep it from becoming too viscous and to prevent the precipitation of the fibrinogen? A 50 per cent dilution was agreed upon.

Should the pH of the plasma saline solution be determined? This was felt to be unnecessary.

What system should be used for transferring the plasma from the pool bottles to the final bottles so as to expose the product to the least danger of contamination, and what type and size of this bottle is the best for the packing and shipment of the solution? The Baxter vacuum system was thought to be the safest and we decided on a one liter Baxter Plasma-Vac bottle as the most advantageous.

At what temperature should the pooled plasma and the plasma saline solution be kept until shipment abroad? Three to 5 degrees centigrade was our decision.

How should the final bottles be labelled, what kind of record card should be kept at the hospitals, and how should the release signed by the donor be worded? These questions were easily answered.

What size carton should be adopted for shipment? It could not be too large because much of the plasma was to be shipped by clipper, and one holding 6 one liter bottles was chosen as the most practicable.

Finally, came the all-important question of bacteriological and toxicity control. This was the most serious problem but it is gradually being settled to our satisfaction. Careful bacteriological cultures of the pooled plasma are first made at the various hospitals—both aerobic and anaerobic —before the addition of the merthiolate solution. If these cultures from the pools are sterile after one week, the merthiolated plasma is added to the saline solution in the final bottles and sent to the warehouse. Simultaneously, a sample from each 2-liter pool in a 300 cc. Baxter Transfuso-Vac pilot bottle is also sent to Meleney's laboratory and from this sample, cultures are made on the third, seventh and fourteenth day and animal tests for toxicity are likewise made. If the culture is sterile and the product is shown to be non-toxic, the bottles of solution from which the sample has been taken are released to the Red Cross for shipment abroad. This technique has worked out quite well but we are still not completely satisfied, and are about to investigate the question as to whether we would not obtain better results by filtering the plasma after converting it into serum by precipitating out the fibrinogen with a calcium salt. This conversion into serum is recommended as plasma apparently can only be filtered with difficulty and serum produced in this manner is thought by many to be safer than serum obtained from the simple clotting of blood. William Thalhimer has very kindly offered his services and the facilities of the Manhattan Convalescent Serum Laboratory to help us study this phase of the problem.

After innumerable meetings and conferences to settle these various questions, toward the latter part of September, the mounting difficulties which we encountered forced us to take a radical step and on October 1, we engaged a full-time, salaried Medical Supervisor to help us solve the technical problems, to formulate a standard, uniform technique and to coördinate the coöperating hospitals. The unanimous choice of the Board of Medical Control fell on Charles R. Drew, formerly of The Presbyterian Hospital and now Assistant Professor of Surgery of the Medical School of Howard University. The School was kind enough

to release him to us for a four months' period. Since Drew, who is a recognized authority on the subject of blood preservation and blood substitutes, and, at the same time, an excellent organizer, has been in charge, our major troubles have vanished. Drew is directly responsible to the Blood Plasma Committee of our Board of Medical Control. This Committee consists of Cornelius P. Rhoads, Chairman, Lester J. Unger and David C. Bull.

We also met some legal snags which the experts in the Department of Health have helped us to unravel.

What was to be done about positive serological tests for syphilis in the blood of these volunteer donors? Should the Department of Health be notified and should the donor be informed? There was no argument about notifying the Department. Section 105, Regulation 14 of the Sanitary Code of the City of New York makes this notification mandatory, but the Department agreed to treat the information discreetly through the agency of Theodore Rosenthal. Informing the donor was considered advisable and the method was left to the discretion of the respective hospital.

Must a complete physical examination including the genitals be made on every donor? This was of great importance as considerably over 50 per cent of the donors were women, many socially prominent and some unmarried. The Department ruled that Section 108, Regulation 5 of the Sanitary Code could be waived in the matter of genital examinations.

Must the Blood Transfusion Betterment Association or the coöperating hospitals obtain a license from the Federal Security Administrator to comply with Section 120, Paragraph 1 of Article 8 of the Sanitary Code? Walter T. Harrison, Chief of the Division of Biologics Control of the National Institute of Health of the U. S. Public Health Service, representing the Federal Security Administrator, ruled for us that he cannot license us or the hospitals as we are not engaging in this project commercially and the Board of Health, which has been most coöperative in every respect, is still taking the matter under advisement. A solution, I am sure, will soon be found.*

Several special research projects in connection with this work have been instituted to be financed through the amount set aside for research, as follows:

* The Board of Health, at its meeting on November 12, 1940, after hearing the report of a subcommittee appointed to study the project, ruled that, inasmuch as it was still in an experimental stage, and as the supervision now in effect appeared to be adequate, no special regulations are called for at this time.

Lester J. Unger has been given a grant to develop an appropriate double needle for withdrawing blood by the closed method and eventually for drawing off the plasma from the original bottle and transferring it to the pool bottle through the same needle.

John Scudder has been given a grant to study the question of centrifugation vs. sedimentation and also to develop an improved dumbbell bottle for collecting the blood.

Cornelius P. Rhoads has developed at the Memorial Hospital an improved apparatus for drying plasma or serum and will probably be given a grant for continuing this study.* It appears that the development of a thoroughly satisfactory method of drying plasma or serum will be the eventual solution of the problem, because of the much greater stability of the dried product, its somewhat smaller bulk, the relative simplicity of packing, storing and transporting it, and the much lesser danger of loss from breakage. We feel that Rhoads' apparatus may be superior to any now in use and our Association is very anxious to assist him in his research in this field.

In addition, the Association also intends, eventually, to encourage and help finance studies, from every angle, on the respective merits of plasma and serum—either liquid or dry—as compared with fresh whole unmodified or citrated blood, and stored blood. We believe that our group has the talent and the facilities, and with the financial aid of the Red Cross and the unlimited supply of volunteer donors furnished by this organization, we should soon be able to settle the major problems in regard to blood substitutes, the best method of their preparation and mass production, and their comparative values.**

In conclusion, may I say that were it not for the broad-visioned sponsorship, and moral and practical support of the Academy, the Blood Transfusion Betterment Association would never have come into being and this constructive project, under its aegis, of giving vital assistance to the one remaining major democracy in Europe, of developing a direct and essential aid for our own national defense, and of eventually helping to solve all the moot points in the entire problem of blood substitution would have been impossible.

* This grant was awarded to Rhoads at the meeting of the Board of Trustees, November 8, 1940.
** The study of one phase of this problem, namely a comparison from the chemical, biological and clinical standpoints of plasma, serum from blood, and serum from plasma—both liquid and dried—was begun by Rhoads, Thalhimer, Scudder and others under the auspices of our Association on November 25, 1940.

GONORRHEA IN THE MALE*

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PERHAPS as far back as medical history goes there has dwelt in the minds of those who cared for the afflicted a decidedly high state of confusion regarding what was the most appropriate treatment for gonorrhea. This confused state has reflected itself in an enormous percentage of the writings upon the subject, to the further bewilderment of those who read. It has, in the past, resulted in the carrying out of a large assortment of treatment methods that were highly inefficient and often caused far more trouble for the patient and his contacts than it was hoped they would relieve. One would be compelled to search far in medicine for any less soundly based therapeutic measures than those that so commonly were employed to cure this disease. It was only necessary for someone to laud a plan of treatment that was just a little easier to carry out, for him to get a multitude of followers. Often it seemed that the more bizarre and lacking in good judgment the plan might be, the more there were who adopted it.

It is not necessary that one be a keen student of this disease for him to discover just why these things were and, to an unfortunate extent, still are. He has but to enquire into the general lack of knowledge regarding the clinical behavior of gonorrhea under varying conditions to see why we have been in such a gullible state that we could be fooled so often. Having revealed this unfortunate fault of the past and wondered why men posted themselves upon these things in all other diseases before they started to treat them, an inquirer naturally would try to determine the present state of things in this regard. And, with all our scientific advances, he would find, to his surprise, that attitudes have not greatly changed. He would discover that the one great cry is, "How should we treat gonorrhea?" He would find reason to be disappointed if he asked many questions about the disease itself. Probably he would cry out himself, "Let's stop this mad rush long

* Presented October 18, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

enough to learn sufficient about gonorrhea to prevent our being perpetually fooled by one writer's dreams and another's faulty clinical interpretations." And, if his cries arrested the attention of us all to the end that we heeded, we would not travel up so many blind alleys or let others make us feel so ridiculous when "the tumult and the shouting dies."

Those who really know gonorrhea are seldom fooled. It is only those whose minds think only of treatment. And, if anyone is of the opinion that the age of gullibility has passed, he has only to look sensibly at what was and is done and said about sulfanilamide for the treatment of gonorrhea to realize that we have not all become so wise as we think. We were told by those whom we thought we could trust that this drug would cure anywhere from 60 to 91 per cent of all ambulatory males who had the disease. Thousands of us read these pronouncements and believed. We analyzed the case tabulations that so often were given and all but a very few failed to discover the "fly in the ointment." And there the fly stood, like Gargantua, grinning at us. It was in the first group of cases that "made" the newspapers and the magazines. And it stood out like the proverbial sore thumb in about every article that cited case reports.

It would not be so tragic if we were the only ones deceived. But the tragedy of the thousands upon thousands of women who have been infected because we did not see what was wrong should be hard for us to forget. Contemplation of this should stir the most somnolent of us into a feverish struggle to learn so much about gonorrhea itself that we never again could be led so widely astray. This is the greatest need of the day so far as this disease is concerned.

Just what was the "fly" in the chemotherapeutic "ointment?" The "fly" was simply this: If sulfanilamide cures gonorrhea, it does it well within the first two weeks of medication and if the patient has a gonococcus after that and eventually gets well—or seems to—he does so for the same reasons that he did before we had sulfanilamide, viz, time and other treatment. Nothing could be more erroneous than to attribute his cure to sulfanilamide. And, yet, we did just that.

What is the real truth about sulfanilamide so far as its effect upon gonorrhea is concerned. This drug does one of three things: (1) It either produces a cure well within two weeks; (2) it eradicates the obvious signs of the disease and leaves the patient as an asymptomatic

gonococcus carrier, or (3) it does not in any way change the course of his disease.

The first question that arises in the mind is: How many does it cure? And the answer is that one has to be generous to a scientific fault to place the figure at as high as 30 per cent, which is a far cry from those romantic figures of from 60 to 91 per cent.

The second question is: How many asymptomatic carriers does it make? To this there is no exact answer but one would be guilty of no exaggeration if he placed his low figure at 20 per cent. He might be more correct scientifically if he placed it much higher.

We can dismiss the definite and obvious sulfanilamide failures by saying that they may be cured by some of our later sulfonamides and those who are not should be treated as cases were treated before these drugs came into use. In other words, we have not reached a point where the best of our former methods of treatment are in any sense outmoded, nor is it probable that we shall for some time to come, if we ever do.

We and Society have little further vital interest in the prompt drug cures and we are not fooled by the obvious sulfonamide failures. But both should be deeply concerned about those who become asymptomatic gonococcus carriers. For a virile male who falsely believes himself cured is a social menace of no small proportions. He brings into the clinical picture a number of things that formerly occupied but a small portion of it. He may go months without any symptoms whatever, despite alcohol and sexual intercourse which, in the presulfonamide days, seldom left him in doubt about the question of cure. When he transmits his infection to a female, she usually, if not always, becomes a totally asymptomatic carrier who has not the slightest suspicion that she has such an infection until she transmits it to a third party. This unfortunate third party is never left in doubt. He has an active infection characterized by a decidedly profuse urethral discharge containing countless gonococci. Interestingly enough, this third party usually registers a prompt clinical response to sulfanilamide medication. That he is not always removed from the seeming endless chain of infection is shown by the fact that he has an equal chance with the "party of the first part" of becoming an asymptomatic carrier.

Thus could the sulfanilamide shaking-down process be continued, if time and space would permit, but it only would bring us to the point reached by the essayist and many of his friends, viz, sulfanilamide is

the poorest of the sulfonamides to use in the treatment of gonorrhea. It should be abandoned for the far more efficient ones, sulfapyridine and sulfathiazole or whatever the future may develop that may be improvements upon them.

As we turn to these better sulfonamides we should do well to avoid the impression that all is "moonlight and roses" and that we can forget the sad lessons of the romance of sulfanilamide. For they, too, produce some asymptomatic gonococcus carriers who can produce others of the same stripe. And there are beginning to return to our dispensaries patients whom we were sure were cured by both drugs some months before—patients who either without exposure, or too often after exposure for the usual incubation period, have developed an urethral discharge containing gonococci. Not only had these patients been subjected to all of our so-called tests of cure but their secretions repeatedly had been subjected to the most careful microscopic and cultural studies.

So far our story has been a decidedly disquieting and gloomy one and it is time to get out into the sunshine, for there is much of it. There are reports by a number of careful clinicians to the effect that the *apparent cure* rate of both sulfapyridine and sulfathiazole runs somewhere between 80 and 91 per cent. And there is little, so far, to suggest that the carrier rate among these *apparently cured* patients is a shockingly high one. Certainly it does not compare with that of sulfanilamide. Even if it eventually proves to be as high as 10 per cent, he who thinks in terms of public health must view the introduction of these drugs into the treatment of gonorrhea as the most glorious thing that has ever happened for its victims. Anything that well within two weeks cures 70 per cent or more of these patients has human values far beyond our powers of expression. None of us ever dreamed that such things would come to pass and, yet, they are here.

So much for the glory and the gloom of it all. Let us draw this to a close with a recital in terse statements of what our clinical experiences have taught us:

1. As blood concentration of these drugs is of no importance, except perhaps in metastatic gonorrhea, large doses are not needed.

2. If the patient is not symptom free by the end of five days, further administration of the same sulfonamide is useless.

3. Change to another may produce results. This is particularly so where sulfanilamide has failed, but reversal to sulfanilamide where the

others have failed is useless.

4. If cure is to be obtained, it takes place probably in the first week.

5. Continuation of the same drug for longer than ten days is of no value.

6. The cure rates of sulfapyridine and sulfathiazole are about the same for both early and late cases.

7. Thus, we can abandon the idea, formerly held by some about sulfanilamide, that results were better in patients who had mustered up some immunity response. The drugs should be started at once.

8. The toxic by-effects of sulfapyridine are, dose for dose, about equal to those of sulfanilamide. For sulfathiazole they are far less.

9. As many of these toxic symptoms appear after the first week of medication, some workers discontinue the drugs at the end of seven days. Their cure rates are not lower than those who continue for ten days or more.

10. With any sulfonamide the patient should be seen by the physician every 48 or 72 hours.

11. In the presence of any toxic symptoms of moment, these drugs should be stopped and the patient instructed to drink large quantities of water to aid in their elimination.

12. Short dosage period and a fluid intake of at least 1500 cc. in the 24 hours will prevent sulfonamide urinary calculosis.

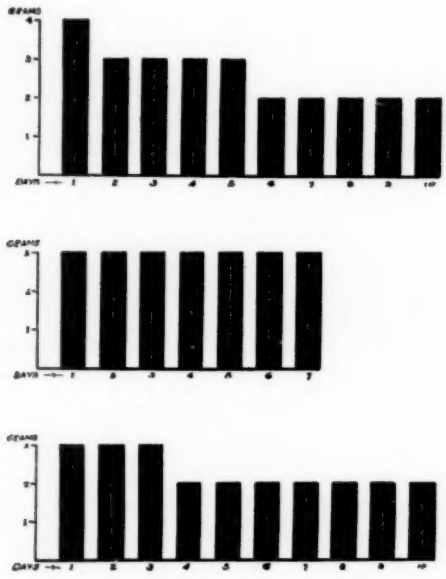
13. Patients seemingly cured have no urethral discharge for study, and in tests of cure the washed urinary sediment which contains urethral, prostatic and Cowper's gland secretions offers the only means of revealing carrier states microscopically.

14. Properly done cultures of carefully collected secretions have twice the diagnostic value of the most carefully done microscopic studies and many times the value of haphazard microscopic methods. Both can fail to reveal persisting infection and should be repeated two or more times.

15. Our older tests of cure, alcohol, sexual excitement and sounds usually fail to stir carrier states into clinical activity in sulfonamide cases.

16. It is felt by some careful clinicians that post-sulfapyridine carrier-states do not lie dormant as long as those produced by either of the other drugs.

17. It is the fixed opinion of most of those who have done most



Schemes of Sulfonamide Dosage Used by Some Careful Investigators with Approximately Similar Results

with cultures as tests of cure that no patient should be dismissed from observation in less than two months during which at least three cultural studies have been made.

18. The lack of the general availability of cultural studies, together with the possibility of infection being missed by even the most careful, should make one hesitate about any highly enthusiastic pronouncements of cure.

19. Under even the best of circumstances it is best to insist that the patient employ rubber sheaths in his sexual pursuits for three months after supposed cure. Most will not do so, but such an admonition relieves the physician of an unpleasant responsibility.

20. At least 30 per cent of all urethral discharges are non-gonorrheal and a microscopic diagnosis of gonorrhea should be made before any patient is started on sulfonamide drugs. They are practically useless in non-specific cases.

In the accompanying chart are outlined several schemes of dosage that apply to each of the sulfonamides and which have given the various workers about equal results.

CURRENT TRENDS IN DIAGNOSIS OF RENAL TUBERCULOSIS*

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DIAGNOSTIC or therapeutic procedures in medicine can never become completely standardized. As the various diseases are understood better, however, some standardization may be accomplished if broad basic principles in diagnosis and treatment can be established and accepted. This would be of distinct value to the medical profession, especially in the teaching of the subject to the medical student. Nowhere would some form of standardization in diagnosis be more welcome than in the subject of renal tuberculosis. The average medical student on graduation has no distinct picture of this disease. One instructor may warn his students against ureteral catheterization to obtain specimens of urine for examination for fear of infecting a normal kidney. Another may advise bilateral retrograde pyelograms in every case of suspected renal tuberculosis. Just what constitutes the indication for nephrectomy in this disease is likewise likely to be very confusing to the young physician. Not at all helpful in the clarification of this subject is the fact that within the last few years diagnosis has been altered radically by the introduction of excretory urography.

Renal tuberculosis has been a recognized disease for a sufficient time and excretory urography has now been used for a sufficient number of years so that it should be possible to evaluate methods of diagnosis somewhat. It may be that if our cases are carefully studied, the trend of diagnosis will be found to be undergoing considerable change. If so, opinions and teaching of this subject may require modification. A correlation of the views of the various schools of thought regarding this disease would be distinctly helpful. Since the advent of excretory urography one group of physicians advocates diagnosis on the basis of excretory urography alone. Others favor cystoscopic examination but differ on the amount of examination of each kidney and on indications

* Read April 17, 1940 before the Section of Genito-Urinary Surgery of The New York Academy of Medicine.

for retrograde pyelography. Opinion varies between members of the extremely radical school who advocate excretory urography alone with no instrumentation and those of the ultraconservative school who insist on multiple cystoscopic examinations if they are necessary, routine bilateral retrograde pyelograms in all cases and examination of ureteral specimens of urine from both kidneys by wet smear, acid-fast stain and inoculation into guinea pigs.

It is my purpose in this paper to determine if possible the current trend in diagnosis in renal tuberculosis and if possible to evaluate the comparative accuracy of the various methods of diagnosis. If this can be done, possibly certain principles in diagnosis will be brought out that will simplify the subject, especially for teaching purposes. The basis for this study is 216 cases of proved renal tuberculosis that have been encountered at The Mayo Clinic during the past five years. The cases are almost consecutive. In the first 100 cases all cases of proved renal tuberculosis were included. This series has been reported in an earlier paper written in collaboration with Braasch. In the remaining 116 cases no case was included in which nephrectomy had been previously performed for renal tuberculosis. This was done so that the study might more nearly mirror the initial diagnostic problem as the patient first consults his physician. From the data obtained it was apparent that our methods of diagnosis in renal tuberculosis have been altered considerably in recent years.

In making such a study the practical aspects must be foremost and the problem must be viewed in its larger aspects. Details and controversial points of academic interest only, must assume the background. For instance, it is not pertinent to such a study whether or not all renal tuberculosis is bilateral, whether or not tuberculous lesions of the kidney heal or whether or not in an occasional case tubercle bacilli, demonstrated in a ureteral specimen of urine, could have been picked up by the ureteral catheter as it passed through the bladder into the ureter. The diagnostic procedures at hand, imperfect though they may be, must be accepted and conclusions must be drawn accordingly. For the purpose of brevity in the remainder of this paper I shall speak of the involved or the more involved kidney as the "bad" kidney. The uninvolved or least involved of the two kidneys will be designated the "good" kidney.

In the analysis of such a problem certain premises must form a basis on which to build. The following statements are generally accepted,

and will serve as the premises of this paper: 1. Tubercle bacilli are not excreted from a normal kidney. 2. Sound diagnosis consists in employing adequate diagnostic procedures to supply sufficient information to insure proper treatment. Fewer procedures are insufficient. More procedures than this are not in the interest of the patient either physically or economically. This is especially true with regard to instrumentation and anesthesia. 3. The clinical term "unilateral renal tuberculosis" is inaccurate as there is no clinical method by which a kidney can be proved to be free from tuberculosis. The four methods of investigating a kidney in the presence of this disease are (1) excretory or retrograde urography, (2) microscopic examination of a ureteral specimen of urine, (3) acid-fast staining of a ureteral specimen of urine, and (4) inoculation of a guinea pig with a ureteral specimen of urine. Although all of these methods are extremely valuable, none are infallible and it is well known that the results of all may be negative even though tuberculosis is present in a kidney. It would be better, therefore, to employ the general term "renal tuberculosis" and to specify the condition of each kidney, stating the type of investigation used to arrive at the diagnosis. 4. The weight of evidence suggests that catheterization of a tuberculous kidney (if carefully done) for the purpose of obtaining a specimen of urine for examination is a fairly safe procedure. Danger of infecting the "good" kidney in this manner is minimal or almost nil. 5. Experience and a perusal of the literature suggest that a retrograde pyelogram of a kidney with an open tuberculous lesion may initiate dissemination of the disease; the most common type of dissemination mentioned in the literature is "tuberculous meningitis." Cases of meningitis following nephrectomy for renal tuberculosis may be the result of the pyelogram before operation rather than the trauma incidental to the operation. Although the danger of retrograde pyelography has been minimized considerably since it has become almost routine to employ media containing organic iodine (as is used in excretory urography), rather than sodium iodide, there is still a definite though small risk accompanying it.

A review of the 216 cases studied elicited some interesting data. In approximately 71 per cent of these cases acid-fast staining of the vesical urine demonstrated tubercle bacilli; this finding suggests that in at least 75 per cent of cases the history, symptoms, physical examination and examination of the vesical urine (properly collected) should establish the presence of tuberculosis of the urinary tract. The problem in the

majority of cases, therefore, is not so much one of determining the presence of renal tuberculosis as it is of determining which kidney is infected or, if bilateral, the degree of involvement of each kidney. Experience at The Mayo Clinic over a period of many years makes us feel that the presence of tubercle bacilli in the urine is indicative of renal tuberculosis and does not occur with any appreciable frequency in genital tuberculosis.

The relative frequency of the various diagnostic procedures employed is of interest. Cystoscopic examination was carried out in 87 per cent of cases and excretory urography in 90 per cent. Diagnosis was made solely on the basis of excretory urography and examination of the vesical urine in 12.8 per cent of cases. In these latter cases supplementary diagnostic methods were not employed because in most of them advanced bilateral tuberculosis could be diagnosed easily from the excretory urogram; in a few, catheterization of the ureters was impossible owing to an impassable ureteral stricture. Catheterization of the ureters to obtain specimens of urine for examination was carried out on either one or both sides in 76.3 per cent of cases. The "good" kidney was catheterized in 67.4 per cent of cases and the "bad" kidney in 46.7 per cent. Retrograde pyelography was employed in only 26 per cent of the 216 cases; retrograde pyelograms of the "good" kidney were made in 11 per cent of cases and of the "bad" kidney in 19 per cent. In only a very occasional case was cystoscopic examination performed more than once for diagnosis. These figures suggest that the trend in diagnosis is swinging toward excretory urography and away from retrograde pyelography; that not more than one cystoscopic examination of as brief duration as possible is being employed in each case and that ureteral catheterization is still employed for the purpose of obtaining specimens of urine for examination in a large percentage of cases.

The reason for this trend in diagnosis may be more fully explained by a more detailed study of these cases. As far as the "bad" kidney is concerned, if the bacillus of tuberculosis has been demonstrated in the vesical urine, detailed visualization in the excretory urogram is not extremely important. By this statement I mean that in the majority of cases the diseased kidney, or at least the more involved of the two, can be determined readily from the excretory urogram. When this fact has been ascertained, nothing more from the standpoint of diagnosis is obtained by attempting to visualize every minute detail by filling and dis-

tending the kidney with media by retrograde pyelography. It must be remembered that diagnosis of renal tuberculosis by excretory urography is somewhat different from that by retrograde pyelography. In a case in which renal tuberculosis is known to be present, as demonstrated by examination of the vesical urine, diagnostic procedures do not need to be pushed to the bitter end in order to demonstrate the pyelographic deformity of cortical necrosis so glibly described in urologic textbooks. A careful examination of the excretory urograms in this group of cases demonstrated the fact that the irregular feathery outline typical of necrosis was by no means the most common finding in the excretory urogram. For instance, of ninety-five "bad" kidneys in which tuberculosis was proved to be present, the excretory urographic findings in order of frequency were as follows: (1) absence of visualization (in 35 per cent of cases), (2) delay in visualization (in 25 per cent of cases), (3) caliectasis, (4) evidence of necrosis, (5) cicatricial deformity and isolation of the tips of calices, (6) deformity and dilatation of the ureter and (7) pyelectasis.

If these facts are kept in mind, the routine use of bilateral retrograde pyelograms in every case of renal tuberculosis may be classed as an excessive and unnecessary diagnostic procedure that is not in the interest of the patient and does not supply sufficient information to justify its use. If a retrograde pyelogram is necessary for diagnosis, however, it is of course a perfectly justifiable procedure. This will be more fully considered later in this paper. Figures 1 and 2 illustrate the fact that complete visualization is not always necessary. In both of these cases tuberculosis had been demonstrated by examination of the vesical urine, previous to urographic examination. In Figure 1 there is marked delay in visualization of the left kidney. Visualization is incomplete but there is marked dilatation of the calices. The right kidney is fairly well outlined and is probably normal. In Figure 2 similar findings are present. It is obvious that a left retrograde pyelogram in either case is entirely unnecessary.

In the case of the "good" kidney the problem of diagnosis is somewhat altered. For this kidney, detail in urographic visualization is considerably more important than it is in the "bad" kidney. In some cases visualization by excretory urography will be sufficiently good to enable the physician to describe the kidney as "urographically normal." In others the visualization may be almost complete, yet the tip of a calix may be indistinct.

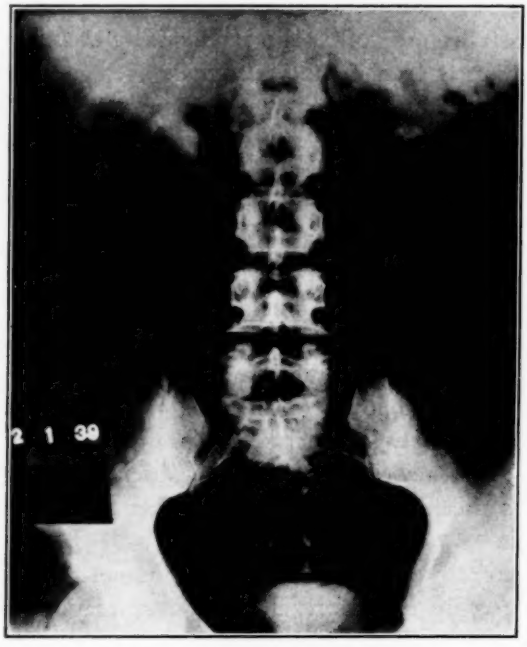

Fig. 1.—Excretory urogram revealing left renal tuberculosis.

These are usually described as "probably normal." In the remainder the kidney is too incompletely outlined for an opinion. The question then arises as to just how normal are the kidneys that are described urographically as "normal" or "probably normal." In 121 of the 216 cases in the series, the "good" kidney was described by the urologist from the excretory urogram as "normal" or "probably normal." Ureteral specimens of urine were obtained from ninety-two of these 121 kidneys. In twenty-four cases pyuria (more than 3 leukocytes per high power field in the centrifuged specimen) was found to be present. Twenty-six per cent of the ninety-two kidneys catheterized were demonstrated to be involved with tuberculosis either by the acid-fast stain or inoculation of guinea pigs. These findings are significant as they demonstrate that catheterization of the "good" kidney to obtain a specimen of urine for examination is highly important if any degree of accuracy in diagnosis is to be obtained. It also illustrates the fact that diagnosis by

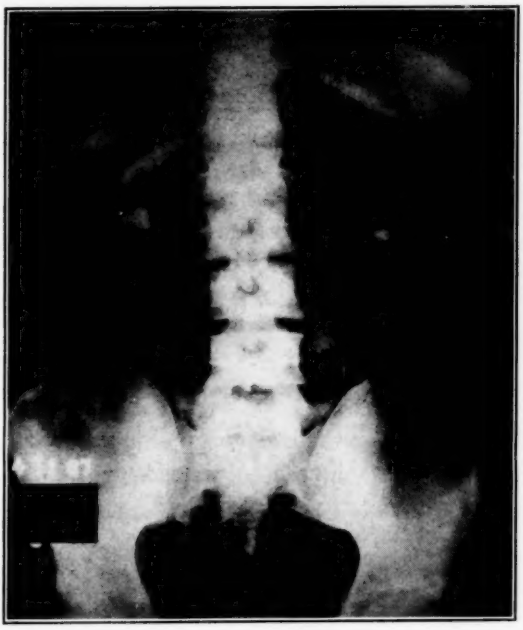

Fig. 2.—Excretory urogram revealing left renal tuberculosis.

excretory urography alone, as advocated by the radical school, is not accurate diagnosis. Whether or not the results of treatment following such an inaccurate diagnosis are good enough to justify employing this method of diagnosis will be considered later in this paper.

Although retrograde pyelography is becoming less important in diagnosis of renal tuberculosis, it still has an important and valuable place. In cases in which the "good" kidney is not visualized sufficiently by excretory urography, it may be necessary to employ retrograde pyelography in conjunction with examination of the ureteral specimen of urine in order to give an accurate opinion concerning the status of the kidney. Just how often this is necessary is open to question. After reviewing the films in this series of cases I am left with the impression that it is not necessary as often as I previously had supposed. For instance, only seven retrograde pyelograms had been made to supplement the excretory urograms of the sixty-nine "good" kidneys in the first 100 cases of this series. At first glance this seems to be entirely

too few, which it may be, and yet a careful comparison of these films with the excretory urograms revealed that a surprisingly small amount of additional information was supplied by them. If the "good" kidney is outlined reasonably well in the excretory urogram, the impression is gained that excretory urography plus examination of the catheterized ureteral specimen of urine gives a remarkably accurate diagnosis. If visualization of the "good" kidney is not good, however, retrograde pyelography is entirely justifiable.

One must remember that up to this point the discussion so far in this paper has concerned primarily the cases in which the diagnosis of renal tuberculosis is relatively simple and is usually made at the initial examination. This comprises roughly about three-fourths of the cases. In the remainder the diagnosis may be difficult, and it may be necessary to employ all methods of diagnosis, including bilateral retrograde pyelograms, to establish an accurate diagnosis. This is especially true in cases of minute early lesions.

From what has been said up to this point certain conclusions may be drawn concerning the accuracy of the various methods of diagnosis. The study suggests that excretory urography will reveal which is the "bad" kidney in a large percentage of cases. In this regard it is very accurate though this information may be supplemented, if necessary, by examination of the ureteral specimen of urine. The excretory urogram will usually suggest the status of the "good" kidney, but here it is inaccurate and inadequate and should be supplemented by catheterization of the kidney, by microscopic examination, acid-fast stain and by inoculation of guinea pigs with the ureteral specimen of urine. This combination of diagnostic methods will yield highly accurate information regarding the "good" kidney, although at times retrograde pyelography is indicated. Bilateral retrograde pyelograms are necessary only in a limited group of cases in which it is difficult to demonstrate the presence of tuberculosis or those cases in which the renal lesions are extremely early or very minute. One cystoscopic examination should be sufficient for diagnosis except in the occasional case. Multiple cystoscopic examinations should be avoided.

Now that the comparative accuracy of our various diagnostic methods has been evaluated, one wonders how accurate diagnosis should be in order to advise proper treatment, or to put the question another way, what preoperative findings should be present before nephrectomy

for renal tuberculosis is advised. This question is not easily answered, for it involves a personal equation both of the physician and patient and requires observation of results of treatment over a period of many years.

In an effort to clarify this subject somewhat Kibler and I made an exhaustive follow-up study of all patients who had undergone nephrectomy at the clinic from 1912 to 1932 inclusive. The results were studied from the standpoint of the findings obtained from investigation of the "good" kidney prior to operation. The results of this study have been fully reported elsewhere, but a few of the more pertinent findings may be mentioned briefly. It was found that 1,131 patients had been subjected to nephrectomy because of renal tuberculosis. These cases were divided into artificial groups depending on the results of the preoperative investigation of the "good" kidney. No attention was paid to the condition of the "bad" kidney, to the length of time the disease had been in progress, or to associated disease, tuberculous or nontuberculous, elsewhere in the body. It was felt that in creating the artificial groups, these other factors would be fairly equally distributed and would not affect the comparative results. Four large groups were created. In group 1 the "good" kidney was not catheterized. In the remaining groups the "good" kidney was catheterized to obtain a specimen of urine for examination. Group 2 indicates that the centrifuged ureteral specimen of urine contained no pus cells or at least less than 3 leukocytes per high power field. In group 3, three to ten leukocytes were found per high power field. In group 4 there were more than ten leukocytes per high power field.

Groups 2, 3 and 4 were further subdivided with regard to the results of acid-fast staining and guinea pig inoculation of the ureteral specimen of urine. Early in the study it became apparent that a negative acid-fast stain of a ureteral specimen of urine was of little significance. Therefore, the subdivisions A, B and C are on the basis of positive acid-fast stains and positive and negative guinea pig inoculation. Subdivision A indicated that no positive acid-fast stains were obtained and guinea pig inoculation was not carried out. Subdivision B indicated that no positive acid-fast stains were obtained and that guinea pigs were inoculated and the results proved to be negative. Subdivision C indicated that positive acid-fast stains or positive results of guinea pig inoculation or both were obtained. In Table I a few of the more

TABLE I

RESULTS OF NEPHRECTOMY IN CASES OF RENAL TUBERCULOSIS: CASES GROUPED ACCORDING TO TYPE OF INVESTIGATION EMPLOYED AND FINDINGS OBTAINED PREOPERATIVELY IN THE "GOOD" KIDNEY

Years After Operation	Group*	Patients Traced		
		Number	Living, Per Cent	Cured or Improved, Per Cent
5	4	45	66.6	44.4
	3	108	56.5	40.8
	2	718	79.7	65.2
	2C	55	58.2	36.4
	2B	209	86.7	75.2
10	4	25	44.0	44.0
	3	87	48.3	39.1
	2	522	65.2	56.4
	2C	30	33.3	30.0
	2B	113	72.6	65.5

* Group 4.—Ureteral specimen of urine contained more than 10 leukocytes per high power microscopic field.

Group 3.—Ureteral specimen of urine contained 3-10 leukocytes per high power microscopic field.

Group 2.—Ureteral specimen of urine microscopically negative (0-3 leukocytes per high power field).

Group 2C.—Ureteral specimen microscopically negative. Tubercle bacilli demonstrated to be present by acid-fast staining or inoculation of guinea pigs or both.

Group 2B.—Ureteral specimen of urine microscopically negative. Results of guinea pig inoculation and acid-fast staining negative.

important groups and subdivisions have been compiled for comparison. It is interesting to note that the more "negative" the "good" kidney is proved to be, the better are the results following nephrectomy. Groups 4, 3, and 2 C contained too few cases to be of statistical value, but they illustrate well the higher mortality and lower percentage of cures when involvement of the "good" kidney can be demonstrated even though the lesion may be minute or extremely early. The best results of course were obtained in group 2 B, which comprises the cases in which no pus was being excreted from the "good" kidney and results of guinea pig inoculation proved to be negative.

TABLE II

LENGTH OF SURVIVAL IN RENAL TUBERCULOSIS: CASES IN WHICH NEPHRECTOMY WAS PERFORMED AND THOSE IN WHICH NO OPERATION WAS PERFORMED BECAUSE OF DEFINITE BILATERAL DISEASE

Years After Operation or Diagnosis	Renal Tuberculosis							
	Bilateral, No Operation, Patients Traced*		Results of Nephrectomy in a Series of 1,131 Cases (1912-1932 Inc.),† Patients Traced					
			Total Series		Group 2‡		Group 2B	
	Number	Per Cent Living	Number	Per Cent Living	Number	Per Cent Living	Number	Per Cent Living
5	148	58.1	1016	74.9	718	79.7	209	86.7
10	133	26.3	753	59.9	522	65.2	113	72.6
15	88	15.9	513	48.9				
20	38	7.9	251	40.3				

* Data collected by Braasch and Sutton.

† Reported previously by Emmett and Kibler.

‡ Group 2.—Ureteral specimen of urine microscopically negative (0-3 leukocytes per high power field).

Group 2B.—Ureteral specimen of urine microscopically negative. Results of guinea pig inoculation and acid-fast staining negative.

If the ureteral specimen of urine from the "good" kidney is microscopically negative, the question is often asked if it is necessary to await the results of guinea pig inoculation before proceeding with removal of the "bad" kidney. To answer this question reference should be made to group 2 C. These are the cases in which the specimen of urine from the "good" kidney contained no pus, but results of guinea pig inoculation proved to be positive. It will be seen that the results in these cases were poor and yet 30 per cent could be classified as cured or improved ten years after operation. The percentage of ten-year survivals in this group, however, is not much better than in those cases of grossly bilateral renal tuberculosis reported by Braasch and Sutton in which no surgical treatment was carried out. The percentage of ten-year survivals in this series was 26.3 (Table II). When the results of operation in renal tuberculosis are being estimated, the results which might have been obtained if no operation had been performed must always be taken into consideration. The answer to this question, there-

TABLE III

RESULTS OF NEPHRECTOMY IN CASES OF GROSSLY BILATERAL RENAL TUBERCULOSIS IN WHICH THE MORE INVOLVED OF THE TWO KIDNEYS WAS REMOVED

Years After Operation	Group*	Traced Patients		
		Number	Living, Per Cent	Cured or Improved, Per Cent
5	3C	15	46.7	20
	4C	12	33.3	0
10	3C	10	40.0	20
	4C	6	00.0	0

* Group 3C.—Ureteral specimen of urine contained 3-10 leukocytes per high power microscopic field. Tubercle bacilli demonstrated to be present by acid-fast staining or inoculation of guinea pigs or both.

Group 4C.—Ureteral specimen of urine contained more than 10 leukocytes per high power microscopic field. Tubercle bacilli demonstrated to be present by acid-fast staining or inoculation of guinea pigs or both.

fore, is a personal matter between the surgeon and his patient. The patient can be advised as to the prognosis and decide whether or not he feels the chances of cure or improvement warrant operation. Most patients prefer to submit to nephrectomy under these circumstances and it is, therefore, probably a justifiable procedure to go ahead with operation without waiting for the results of the animal inoculation. Even if such a course is pursued, however, the guinea pig inoculation should be done to permit a more accurate prognosis and to assist in deciding on the type of postoperative care to be given the patient.

When there is a definite open lesion in the "good" kidney which is excreting pus cells and tubercle bacilli, the results of surgical treatment have been extremely poor. This is especially true if any urographic deformity can be demonstrated. In Table III the results in this type of case are given. Occasionally a patient is seen who has bilateral renal tuberculosis and such pronounced vesical symptoms that the surgeon feels removal of the worst kidney may give some relief. Experience at the clinic with this type of surgical procedure is extremely discouraging and we feel that it should be avoided whenever possible.

Referring again to the inaccuracy of the clinical use of the term "unilateral renal tuberculosis," Table I is of especial interest. It would

depend on the school of thought to which one adheres, which of these groups should be classified as "unilateral renal tuberculosis." For instance, the radical school, which depends almost entirely on excretory urography for diagnosis, might include all of these groups under the term "unilateral," whereas the ultraconservative school would speak only of cases in group 2 B as unilateral. From the postoperative results, it is apparent that even group 2 B contains cases in which tuberculosis must have been present at the time of diagnosis, even though it was not detected. If larger groups of cases throughout the country could be studied from this point of view and the data pooled, the information obtained would be invaluable. The process of teaching the medical student would certainly be simplified, for he could be taught the relative accuracy of the various methods of diagnosis, and the average results of treatment that might be expected depending on the type of investigation and findings obtained. With such information he could then rely on his own judgment and with confidence and self-assurance decide on methods of diagnosis and treatment rather than follow with blind faith the dogma of his instructor. It must be remembered, of course, that treatment in any disease can never be determined automatically by reference to statistical tables after diagnosis has been completed. Each case must be individualized and the physician must temper his judgment with such factors as the general condition of the patient, the length of time the disease has been in progress and the presence or absence of associated diseases.

Summary

Sound diagnosis in any disease implies that adequate diagnostic procedures have been employed to obtain sufficient information to insure proper treatment. Fewer procedures than this are insufficient. More procedures are not in the interest of the patient either physically or economically. An analysis of the methods of diagnosis employed in 216 cases of renal tuberculosis encountered at the clinic in the past five years suggests that the trend of diagnosis is away from retrograde pyelography and toward excretory urography. An appraisal of the various methods of diagnosis employed in these cases suggests that in the majority of cases accurate diagnosis can be made by means of excretory urography and one cystoscopic examination for the purpose of obtaining specimens of urine from the good kidney and at times both

kidneys to be examined microscopically as a wet smear, with the acid-fast stain and by inoculation into guinea pigs. It is seldom necessary to perform more than one cystoscopic examination on each patient. Multiple cystoscopic examinations are to be avoided. Retrograde pyelograms of the "good" kidney may be indicated when visualization by excretory urography is not adequate. In the average case retrograde pyelograms of the "bad" kidney are not necessary even though visualization by excretory urography is incomplete or absent. There is a small group of cases, however, in which the diagnosis of renal tuberculosis is difficult and in these cases bilateral retrograde pyelograms must be employed. The routine use of bilateral retrograde pyelography in every case of suspected renal tuberculosis is to be condemned as an unnecessary diagnostic procedure which is not in the interest of the patient.

With the comparative accuracy of the various diagnostic procedures evaluated, an attempt has been made to answer the question of how accurate diagnosis must be and what findings must be obtained in renal tuberculosis to assure satisfactory results from nephrectomy. A brief summary of the late results in 1,131 cases of renal tuberculosis in which nephrectomy was performed was used as the basis on which to answer this question. The study was based on the type of investigation used and the findings obtained in the preoperative investigation of the "good" kidney. The study demonstrates the inaccuracy of the clinical term "unilateral" renal tuberculosis and illustrates the fact that the more "negative" the "good" kidney is proved to be, the better is the prognosis for the patient following nephrectomy. The study emphasizes the need for accurate diagnosis in each case to enable the physician to give the patient a fairly accurate prognosis and to decide on proper preoperative and postoperative care. From the tabulated results of a large series of cases such as is presented herein, physicians should be better able to judge in which cases nephrectomy is justifiable. If more cases from large clinical centers could be studied from this point of view and the results pooled into one tabulation the information would be of still greater value.

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THE TREATMENT OF RENAL TUBERCULOSIS*

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THE treatment of renal tuberculosis is an important subject because of its public health aspects as well as its general medical considerations. When we know that not less than a million and a half people have active tuberculosis, of whom, most conservatively, 5 per cent have renal involvement, the magnitude of the problem of furnishing adequate medical care is apparent.

The public health interest lies in controlling the tremendous economic loss incurred through deaths and physical disabilities incident to this disease. Let us take a rapid survey of the vital statistics and medical facilities available for the treatment of this condition. To begin with, many of our larger centers of population do not have vital statistics which furnish accurate data concerning the incidence or death rate of renal tuberculosis. One municipal tuberculosis sanatorium in one of the most important cities in our country cannot report the incidence of renal tuberculosis nor its death rate because of lack of resources. Many of the health departments have no definite policies in regard to the method of handling cases of renal tuberculosis. The census reports of deaths due to renal tuberculosis are only as accurate as the local reporting of the disease and these are very variable.

The United States Public Health Service and the Social Security Administration, both of which are cognizant of conditions, have comprehensive plans to furnish adequate medical care for tuberculous patients which it is hoped will carry along with it adequate urological care.

The Social Security Program is estimated on a cost basis as follows:

1. For construction of 79,515 hospital beds at $3,500 per bed	$275,302,500
2. For annual maintenance of 79,515 hospital beds	59,636,250
3. For x-ray examination of family contacts of 862,596 known cases of tuberculosis at $7.00 each	6,038,172

* Read April 17, 1940 before the Section of Genito-Urinary Surgery of The New York Academy of Medicine.

The report of the Technical Committee on medical care to the National Health Conference which was held in July, 1938, had the following plan presented by the Public Health Service.

Construction	$15,000,000
Three years maintenance	6,000,000
Annually available for other elements of the tuberculosis program	43,000,000

These figures show how important the Social Security and Public Health authorities consider the problem of medical treatment for tuberculosis patients. We should make it our duty to interest ourselves in this problem and bend every effort to control a disease which is so great an economic drain on our country.

The general medical-surgical consideration of the treatment of renal tuberculosis calls for a comprehensive understanding of many factors which are involved in each case. The following factors should be taken into consideration and appropriate measures taken:

1. Extent of renal process:
   a. Miliary
   b. Necrotic destructive
   c. Nephritic
2. Extent of extrarenal lesions:
   a. Bilateral involvement
   b. Bladder involvement
   c. Genital involvement
   d. Pulmonary
   e. Other extraürinary lesions
3. Factors affecting general resistance:
   a. Economic
   b. Psychologic
   c. Climatic—ultraviolet
   d. Pain
   e. Coëxisting bacteriuria
   f. Food
   g. Medication, tonics.

Extent of Renal Involvement

Whether the condition is (1) one of tuberculous nephritis, which should be interpreted as indicating non-destructive minimal lesions, (2) destructive parenchymatous or (3) acute disseminated miliary is

the first consideration. The tuberculous nephritic patients should be treated medically and all measures to conserve and build up the general resistance instituted. The destructive parenchymatous lesions are the ones which call for our keenest judgment. The destructive parenchymatous processes which involve any more tissue than one minor calyx should be subjected to nephrectomy unless there are serious contraindications to surgery from a risk standpoint. The patient with a slight involvement of one minor calyx is our greatest problem—should nephrectomy be performed or should he be subjected to medical regime? This depends of course upon whether renal tuberculosis heals. There seems to be no sound reason for maintaining that tuberculosis does not heal. Tuberculous processes heal in every other tissue. The cures of the nephrectomized patients run well above the known incidence of bilateral involvement. I have observed patients of my own with involvement of solitary kidneys in whom the tuberculous process has become arrested. In the absence of special indication, the minimal lesions in single calyces should be treated with rest and building up of resistance. The acute miliary lesion should not be treated surgically because it is bilateral and usually a terminal fatal process.

Extent of Extrarenal Lesions

Bilateral destructive lesions usually call for medical treatment. In instances in which one side is extensively involved and productive of appreciable distress and the other side has minimum involvement, nephrectomy of the bad kidney is indicated.

When the bladder symptoms are severe and progressive, nephrectomy is indicated. Persisting bladder symptoms call for the following treatment, in order of relative risk: urinary antiseptics for mixed infections; caprokol, when tolerated and effectual; increasing strength of phenol lavage, when effective, up to 6 per cent; intrathecal alcohol injections; presacral neurectomy; ureterostomy; ureterosigmoidostomy.

When genital involvement coëxists, these lesions should be treated with medical measures until they become destructive at which time they should receive appropriate surgical treatment. There does not seem to be justification for early extensive removal of the seminal tract.

When pulmonary involvement exists, appropriate measures should be instituted. There is no objection to keeping the open pulmonary patient with other open cases but it is not justifiable to put patients with

closed lesions with open ones, which is unfortunately frequently done. Osseous, glandular and gastrointestinal lesions call for appropriate treatment and modify our advice in the renal problem. Tuberculosis of the central nervous system is always fatal and usually rapidly so.

General Resistance

The general resistance factor is the vital influence, as it is this factor which determines the course of each case. Every effort should be made to influence the general resistance favorably. The Social Security Administration is interested in improving the economic status of masses of the people. Our first interest then should be directed to improving the general living conditions both collectively and individually.

The individual who is the breadwinner will not and in many instances cannot be taken out of circulation with our present economic setup. The psychological factors are important in progress, in that a depressing psychological status retards recovery. The importance of this factor should not be minimized and real effort should be devoted to psychic treatment.

The climate is important. In the Southwestern states and Central American countries the incidence is low for genitoürinary tuberculosis, and Dr. Boyd, the present President of Panama, states that there is no genitoürinary tuberculosis in Panama. Whenever possible patients should be put in an advantageous position by living in these climates both before, during and after surgery. Ultraviolet radiation in conservative dosage is good when pulmonary involvement does not exist.

The question of diet is very important. Cod liver oil, plain, if tolerated, or its concentrate, if not, with at least one quart of milk a day should be given in conjunction with a generally wholesome diet.

Coëxisting infections of the kidney and bladder are more effectively combated now than ever before. Nearly all bacteria except the Streptococcus fecalis respond to the sulphones, and mandelic acid is equally effective on all except the Escherichia coli. Control of the complicating infections makes the difference between comfort and discomfort and between improvement and retardation.

Bed rest is of paramount importance both before and after surgery, if surgery is done, and the amount of bed rest should be judiciously directed to suit the indications in the individual case.

Sanatorium or equally satisfactory housing care with abundant rest

should be provided for all patients for at least a year following nephrectomy or until there is indication of cessation of activity of the lesion which is being treated medically.

Conclusion

All effort possible should be expended in making available adequate facilities for treating renal tuberculosis in order to materially lessen the incidence and mortality.

Bed rest and the many details utilized in building resistance with or without and before and after surgery are the most important single factors in the treatment of renal tuberculosis.

GONOCOCCAL INFECTIONS OF WOMEN*

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THE extraordinary results obtained in the experimental five day treatment of early syphilis have distracted attention from the equally remarkable progress recently made in both the diagnosis and treatment of gonococcal infections. This treatment of syphilis can only apply in the early stages of infection and requires hospitalization under the constant observation of a trained staff. It is not generally realized that effective methods of handling gonococcal infections, requiring only ten to twelve days of treatment, have been developed. With such methods, probably four-fifths of our patients can be cured, and they are effective in treating acute or chronic gonococcal cases without the necessity of hospitalization.

In this country we have about a million cases of gonococcal infections annually. It is estimated that about 250,000 of these occur in women. In the past, all forms of treatment have been remarkably unsuccessful. The policy has been one which amounted to little more than watchful waiting for the spontaneous recovery of the patient, with surgical interference when necessary. Nelson has aptly said that the newer sulfonamide therapy returns the treatment of gonococcal infections to the general practitioner, with the gynecologist performing only the function of an occasional consultant.

Accurate diagnosis of gonococcal infections has always been difficult. The fact that spreads (smears) so rarely detect the characteristic Gram negative intracellular diplococcus has discouraged us unduly. Improvements in methods of culturing the organism have made it possible to recognize many cases that formerly could not be detected.

In most acute cases of cervicitis both positive spreads and cultures are usually obtainable. A careful technique must be observed in taking swabs from the cervical canal or urethra if positive spreads or cultures are to be secured in any considerable percentage of cases.

* Read October 18, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

If swabs are to be taken from the urethra for spread or culture, the patient should not have voided during the preceding hour. The urethra should be massaged toward the meatus and the swab inserted directly into the urethra and turned about well within its lumen.

When taking swabs from the endocervix, use no lubricant on the bivalve speculum. Cleanse the external os and canal with dry pledgets of cotton and insert the sterile swab well up into the canal. Grip the cervix between the blades two or three times to express all possible organisms from the lining glands into the cervical canal. Merely twirling a swab in the vicinity of an infected cervix or urethra is common practice and is nearly always unsuccessful in getting positive results.

If culture plates are at hand the cultures should be made immediately. If delay is necessary, drop the swab into a sterile tube containing 2 or 3 cc. of proteose peptone Number 3 broth. Transfers to culture media must then be made within 6 hours at the most.

As the acute phase of the infection wears off, it becomes increasingly difficult, and may even prove impossible, to secure positive spreads. In this stage of infection, as Carpenter[1] pointed out, cultures will prove positive more than twice as often as will spreads. Spreads at the best, even in the hands of experts, are unreliable. In some cases cultures will regularly be positive while spreads are negative.

A diagnosis must depend on:

1. Positive spreads or cultures
2. The clinical appearance of the cervix and possible tubal involvement
3. A carefully taken history of the patient

While positive cultures are conclusive evidence of gonococcal infection, such cultures are not always obtainable. One may be forced to make a diagnosis on a history of intercourse with an infected partner followed by leukorrhea and other clinical symptoms.

Careful laboratory work should not be omitted. As an illustration of the difficulties of diagnosis, in the New Haven Hospital cultures were taken from the cervices of eighty patients in whom gonococcal infections were suspected. Only six of these proved positive. Mahoney also reported taking spreads and cultures from 1598 prostitutes who were presumably infected. Spreads proved positive in only ninety-seven of these while cultures were positive in 21 per cent of the group. However, without access to cultures, gonococcus infection cannot

today be adequately handled. Unfortunately, only a few of us have access to the necessary laboratory facilities.

There is no one reliable provocative test which can be relied upon to produce positive laboratory evidence in cases of latent infection. Handling the cervix, or local application of any irritating material such as glycerine or silver nitrate, may provoke a discharge of latent gonococci.

Unfortunately, complement fixation tests are of little or no value in making a diagnosis, although a strongly positive complement fixation test which becomes negative as symptoms disappear, suggests a cure. If the test remains positive under similar circumstances, it may be regarded as suggestive evidence that gonococcal infection still remains.

As we look back on the methods of treatment only recently in vogue, we must realize that none of them could possibly have had any real curative value. In acute urethritis we were careful to avoid treatments that risked spreading the infection to the cervix. If an acute endocervicitis developed, strong antiseptics were avoided lest the tubes become involved. As the infection subsided, antiseptics were applied to the cervical mucosa. On reflection, we realize that gonococci invariably live in the depths of and beneath the mucosa, and that no applications to the surface can possibly reach them in their habitat. The risk of spreading gonococcal infection to the tubes by trauma of the mucosa in the name of treatment contraindicates the use of local antiseptic applications. With modern chemotherapy the cervix usually improves so rapidly that there would be no place for local treatment even if it were beneficial.

Vaginal douches can do nothing more than wash out the offensive secretions from the vaginal vault. As treatment, douches are comparable to the use of a handkerchief in a case of acute rhinitis. It is true that the warmth engendered in the pelvis by the use of hot douches often renders patients with acute salpingitis more comfortable.

The use of the Elliott apparatus or diathermy constituted an improvement on the douche in bringing heat to the pelvic structures. Both undoubtedly gave relief from pain and often hastened resolution in cases of tubal infection. It is noteworthy that the Strong Memorial Hospital in Rochester, where they were in constant use, has abandoned them entirely for chemotherapy.

A host of other non-surgical methods of treatment have been tried

and found wanting. Among them I may mention Gellhorn's non-specific protein therapy for subacute salpingitis, iontophoresis and vaccines. The latter will produce a positive complement fixation test but does not cure or improve gonococcal infections.

In the treatment of non-specific cervicitis, the use of a cautery is of the greatest value. It cannot be too strongly emphasized that its use in gonococcal infections is illogical and unpardonable. It is true that linear cauterization will decrease the amount of mucopurulent discharge. It cannot possibly destroy all the gonococci which thrive between the areas of coagulation. The danger of producing an extension of a localized infection to the tubes far outweighs the possible benefits of symptomatic relief. No endocervix should be cauterized while gonococci are demonstrable. Use of the cautery in secondary infections after gonococci have been eliminated is often most helpful.

For a long time we have realized that endocervical gonococcal infections tend to die out in 6 months or less if tubal infection does not intervene. In an effort to determine this point, Mahoney selected a group of sixty imprisoned prostitutes, in all of whom positive spreads and cultures could be obtained from the cervix. Laboratory determinations were made every 48 hours. At the end of 40 days, all spreads and cultures in the entire group were negative, although no treatment of any kind had been given. It is evident to me that in the past we have credited our methods of treatment with the cure of patients who were, in reality, all curing themselves. I firmly believe that they recovered, not because of our interference, but in spite of it. At present we use no local treatment whatever, but rely on sulfapyridine or sulfathiazole to cure our patients.

Treatment

The only generally recognized curative methods of treatment of gonococcal endocervicitis and salpingitis at our disposal are:

1. The use of artificially produced fever, or better
2. Appropriate sulfonamides given in adequate amounts.

The Kettering hypertherm apparatus or its equivalent was the positive method of treatment par excellence only a few years ago. A high percentage of cures can be, and undoubtedly have been, produced by this method. Unfortunately, hyperthermia is time-consuming, uncomfortable and expensive for the patient, as well as dangerous, if not ad-

ministered under the constant supervision of a carefully trained staff. It now finds its place in the treatment of cases in which the sulfonamides have failed to cure. Its value in the treatment of gonococcal arthritis is probably as great as that of the sulfonamides. In the Rochester Clinic, where hyperthermia was in constant use only recently, it has been abandoned, except for use in the sulfonamide failures. In these cases it is often of great value.

Sulfonamide Treatment

While excellent results were obtained by treatment with sulfanilamide as evidenced by reports of series of cases with a rate of cure varying from 30 per cent to 90 per cent[2] or more, the better results are only obtainable with patients kept under most careful supervision in the hospital. Fractional administration of the drug during day and night were necessary, and the frequent production of toxic symptoms made adequate sulfanilamide treatment a nightmare for both patient and physician.

If ambulatory treatment was attempted, it usually met with very unsatisfactory results. Fear of, or the actual development of toxic symptoms, prompted the physician to reduce the dose of sulfanilamide to the point of easy tolerance. As a rule, patients were rather rapidly relieved of their clinical symptoms, gonococci could not be demonstrated by laboratory methods, and the case was only too often pronounced cured before a relapse made him or her an uncomfortable menace to society. It is estimated that not more than 30 per cent of ambulatory patients were cured with sulfanilamide. Sulfanilamide has no longer a place in the treatment of gonococcal infections, except for a very limited field in treating cases which have not been cured by other much more potent preparations, i.e., sulfapyridine or sulfathiazole.

Since sulfapyridine became available, an increasing number of enthusiastic reports on its efficacy in gonococcal infections have appeared. The fact that the drug can produce all the toxic symptoms resulting from large doses of sulfanilamide, plus serious kidney complications, at first greatly decreased its sphere of usefulness.

Studies by Mahoney and Van Slyke of the U. S. Public Health Department, and various other clinics, have shown that sulfapyridine, if given for from 10 to 12 days in divided doses of 0.5 gram every 4 hours,

[2] Nimelmann et al[3] and Douglas[4] report 94 per cent cures.

four times daily (not exceeding a total daily dose of 2 grams) is not commonly toxic. Serious toxic symptoms resulting from such doses are extremely rare. Moreover, the percentage of cures arrived at by this treatment is almost as high as that resulting from dangerously large doses.

Patients treated in the manner just described must be impressed with the extreme importance of taking their tablets regularly at the hour advised. Neglect of this particular, courts failure. While taking the drug in this way, hospitalization is unnecessary, and there is no need to limit fluid intake.

During the course of treatment, we make it a rule to give patients only eight tablets at a time, enough to last for 2 days. The patients are seen and examined at 48 hour intervals. If toxic symptoms are encountered, or if anuria, hematuria or renal pain should develop, treatment must be stopped.

Ordinarily, cases of gonococcal endocervicitis under the treatment that we are discussing will show obvious improvement in from 48 to 96 hours. The purulent discharges decrease very quickly. The cervix, which is usually red and swollen, rapidly assumes a normal appearance. It is uncommon to find either positive spreads or cultures after 48 hours of treatment. If no improvement is evident after 5 or 6 days, the drug should be stopped for a few days and a change made to sulfathiazole. The latter is administered in the same dosage as is sulfapyridine. Frequently, patients appear entirely well by the end of 4 or 5 days. Even if this be the case, treatment should be continued until it has been given for 10 or 12 days. We have regularly insisted on having our patients continue for 12 days. The results are usually so extraordinary that the physician who is familiar with the ordinary course of gonococcal infections can hardly believe the clinical evidences of improvement and cure.

When the dosage of sulfapyridine is kept below 2 grams per day, serious toxic symptoms rarely develop. Mild headaches, anorexia or slight nausea are frequent, but do not often necessitate cutting short the treatment. Blood counts and urine analyses made at each visit are a safeguard, although some clinics have dispensed with them without disastrous results.

Blood concentration studies are of interest for the purposes of making scientific studies. They are not necessary for the ordinary

practical treatment of patients. With a daily total of 2 grams of sulfapyridine or sulfathiazole, every patient studied has absorbed enough of the drug to be effective. A certain amount of variation of the concentration of the drug has been found, but in repeated studies it has not been possible to find any relationship between cures and blood concentration when this level of drug intake has been maintained.

Toxicity

All of us are familiar with the possible toxic effects that may result from the administration of sulfapyridine. In treating 200 hospitalized males with rather large doses of sulfapyridine, Mahoney found that only 10 per cent were free of any toxic symptoms and that about 7 per cent or 8 per cent of these cases might be rated as "severe." In studying 100 patients who received 3 grams of sulfapyridine on the first day and 2 grams on the subsequent days of treatment, about 60 per cent showed some slight evidence of toxicity; three developed severe headaches and one, severe nausea. Among the milder evidences of toxicity, Mahoney lists insomnia (15 cases), anorexia (15 cases) and mentions other symptoms of relative unimportance. One patient had an idiosyncrasy to the drug which necessitated stopping treatment. In only this one patient, among the 300 patients treated, was it necessary to stop therapy on account of toxicity.

In treating 650 women with gonococcal infections at the New York City House of Detention, Nimelmann has given the usual dose of 2 grams daily for 8 days. In this series there have been a few toxic manifestations, including slight headache, nausea or occasional vomiting. There have been no renal disturbances caused by the drug and no critical blood dyscrasias.

Using larger doses of sulfapyridine (5 grams for 3 days and 3 grams for 4 days) E. D. Barringer, Horowitz and Strauss were obliged to stop treatment on account of toxic symptoms in 12 of a group of 100 patients so treated.

In our own limited experience, patients given doses of 2 grams of sulfapyridine per day are often conscious of some mild sensations such as sleepiness, faintness, anorexia, which do not warrant stopping therapy. One private patient bought her own sulfapyridine and did not return for observation. She took 5 grams daily for 10 days before returning to us cured of gonococcal infection but suffering from violent gastro-

intestinal symptoms.

Patients treated with sulfapyridine commonly develop a relative monocytosis while the hemoglobin and red count usually show only minor variations. It is inadvisable to treat patients with sulfonamides in whom the hemoglobin figure is below 50 per cent. It should be mentioned that pregnancy is not a contraindication to the use of the sulfonamides.

Results of Treatment with Sulfapyridine

Ordinarily, improvement or apparent cure is evident in 5 or 6 days. If a given patient is then unimproved, the use of a different drug is indicated. The fact that a patient has been treated with sulfanilamide and not cured, only slightly decreases her chance of cure with sulfapyridine. Many such cases have been successfully treated. Rarely, patients may not appear cured until 2 or 3 weeks after treatment is completed.

The high standard for evidence of cure suggested by the American Neisserian Society requires that:

1. Spreads and cultures taken at 2 week intervals shall remain consecutively negative for 4 months
2. The cervix must appear normal
3. Leukorrhoea must be cured, or at the most, should amount to no more than a small amount of clear mucus.

For obvious reasons, the exact fulfilment of all these requirements is difficult or impossible to carry out faithfully in any large number of consecutive cases. For purposes of scientific accuracy, I shall use the term "apparent cures" in quoting statistics hereafter. In the different studies to be mentioned, careful reëxaminations of patients have been combined with many repeated laboratory studies of spreads and cultures.

Apparent Cures—With Sulfapyridine

1. E. D. Barringer, Horowitz and Strauss; 100 cases: Apparent cures—67 per cent. Dosage—5 grams for 3 days; 3 grams for 4 days.
2. J. F. Mahoney and Van Slyke have more than 80 per cent of apparent cures in women, using a dose of 3 grams for 1 day and 2 grams of sulfapyridine on subsequent 7 days.
3. In the New York City House of Detention—Nimelmann in consultation with Mahoney and Van Slyke has treated 650 women

with gonococcal infections. Two grams of sulfapyridine were given daily for 8 days. About 80 per cent of these cases are in the "apparently cured" group.*

There can be no doubt of the great efficacy of sulfapyridine in the treatment of gonococcal infections.

Sulfathiazole

During the past year, numerous reports of the extraordinary results achieved in the treatment of pneumonia with sulfathiazole have appeared in the literature. The results here have been so spectacular that prior to the very recent appearance of the drug on the market, but little was obtainable for investigative work in gonococcal infections.** Consequently, I can only report the results of a limited number of cases treated under the supervision of J. F. Mahoney of Staten Island, Fred Adair of Chicago, and myself.

In New Haven, over fifty patients with gonococcal infection have been treated with sulfathiazole during the past 4 months by myself and my associates. Thirty of these were women. A standard dosage of 2 grams per day (i.e., 0.5 gram given at 8.00 a.m., 12.00 m., 4.00 p.m. and 8.00 p.m.) has been given every patient for 12 days and no longer. All of us have noted that fewer patients complained of toxic symptoms than is the case when sulfapyridine is prescribed. Transitory malaise, mild headaches, or anorexia have been common, but in no case have severe toxic symptoms necessitated suspending treatment. We have not seen any urinary disturbance or blood dyscrasias. In the majority of our patients it has not been possible to have routine blood counts and urine examinations performed.

As we have only been using sulfathiazole for 4 months, I can only speak of "apparent" results, although patients who appear cured for 2 months after sulfonamide treatment commonly remain cured. All of the thirty women treated showed marked clinical improvement within 5 or 6 days at the most after treatment was begun. All of them soon developed negative spreads or cultures. Two patients did not complete their courses of treatment and had to be re-treated. Two patients, after apparent cure, showed spermatozoa in the spreads taken from the cervix. Both admitted intercourse with infected partners and

* For references and summary of results in 1745 cases of gonococcal infections treated with sulfapyridine and reported by 22 different authors, see the report by Van Slyke, Wolcott and Mahoney.[5]

** By the courtesy of E. R. Squibb & Sons, the author has been supplied with sulfathiazole for the treatment of gonococcal infections since June 1940.

both developed what we may fairly call re-infections. One patient with acute salpingitis was rapidly cured of her tubal disease, but some weeks later developed a Bartholinitis. In the remainder of our patients, discharges rapidly disappeared and spreads and cultures remain negative. It is reasonable to believe that 90 per cent or more of the group are cured. Obviously one must keep patients from having intercourse with infected partners, or anyone else if possible. This is far easier said than done!

Adair[6] reports that in his clinic seventy-one women have been treated for gonococcal infections with sulfathiazole. Fifty-five of them were followed and of these forty-five appear to be cured. Five at least and possibly ten of his patients appear to have contracted re-infections while under observation.

Mahoney[7] has treated 125 patients with gonococcal infections with sulfathiazole—105 men and 20 women. None of his patients suffered from toxic symptoms sufficient to keep them from the activities of every day life. It is interesting that in the male group 91.1 per cent were cured. All twenty women in Mahoney's series rapidly yielded negative spreads and cultures. All showed evidence of clinical cure. He estimates the rate of cure in this group as 90 per cent or better.[8]

Sulfathiazole is less toxic than sulfapyridine and is consequently more easily administered. The high rate of apparent cures in the relatively small number of cases reported suggests that it is apt to supplant sulfapyridine in the treatment of gonococcal infections.

Salpingitis

In dealing with gonococcal infection, one must always remember that its normal habitat is found in and under the mucosa. This is true in tubal as well as in cervical infections. Pyosalpinx or hydrosalpinx not infrequently follows an attack of gonorrheal salpingitis. Formerly the tubal contents were deemed sterile in these cases. More recently, Studdiford and others have shown that gonococci may be cultured from pus tubes removed long after the initial attack.

A correct diagnosis of acute gonococcal salpingitis is usually made without great difficulty. The history and the fact that it is almost invariably bilateral and usually accompanied by an obvious cervicitis, ordinarily make it a simple matter to come to a correct conclusion. We have all learned that operative interference is dangerous and unwise

until acute symptoms have subsided. A modified Fowler's position, hot douches, ice bags with fluids and supportive treatment used to be our mainstays. If a pelvic abscess developed, its evacuation and drainage through the vaginal vault was indicated, as it is today. Subacute or chronic salpingitis was treated with non-specific protein therapy, which was later discarded as unsatisfactory. The development of diathermy enabled us to introduce heat into the pelvic structures and proved of real value. Many patients were relieved of pain more adequately than could be done even with opiates. There is also good evidence that inflammation subsided, pelvic masses diminished and resolution took place more rapidly than under any other then-known form of treatment. If a patient had suffered with former attacks of salpingitis, operation was, and is still, often indicated a week or more after the temperature returns to normal. Ordinarily under such circumstances a supravaginal hysterectomy combined with a bilateral removal of the tubes is indicated, if it is judged wise to operate at all. The ovaries should not be removed if their condition warrants leaving them in situ. In judging whether to operate or not, one must consider the age of the patient, her past history, her situation with regard to children, as well as her symptoms, unless the amount of pelvic pathology dictates the decision. It must be remembered that while an attack of gonococcal salpingitis often or even usually renders a woman sterile, such is by no means always the case. I have seen one patient who became pregnant 6 months after I had myself drained a large pelvic abscess which resulted from a gonococcal infection of the tubes. When operating, one is often tempted to try conservatism by sparing one tube which may appear less affected than its mate. Doing so, or performing partial resections of tubes is nearly always a mistake. We have all had occasion to regret overconservatism and have rarely regretted the performance of a complete removal of both tubes when it was indicated.

If both ovaries are removed of necessity, the patient—usually a young woman—may later suffer severely with symptoms of an artificial menopause. In these circumstances, headaches, vertigo and vasomotor symptoms can often be made tolerable by the administration of estrogens. Stilbestrol given orally in doses of 1 to 5 milligrams per day often gives extraordinary relief. If this produces toxic symptoms, hypodermic administration of other estrogens may be necessary. Luminal given by itself may serve our purposes.

Use of Sulfapyridine and Sulfathiazole in Gonococcal Salpingitis

Sulfapyridine and sulfathiazole are rapidly revolutionizing the treatment of all forms of gonococcal infections. Their exact modus operandi is not clearly understood, but is supposed to depend partly on their ability to stimulate an immune reaction and partly on an ill-defined inherent action as an antiseptic. Cases of acute and subacute salpingitis respond to treatment with these drugs in what is often a dramatic manner. The amount and method of giving them is the same as that just recommended for gonococcal endocervicitis. Our own experience with the use of sulfathiazole includes only six cases classified as acute or subacute. In 2 to 3 days, and at times much sooner, after treatment was initiated, pain and fever nearly or quite disappeared. The relief of pain is apt to be commented upon by the patient within 12 or 24 hours of the institution of therapy. So striking is the improvement that diathermy or opiates need not be used. The tense abdomen quickly relaxes and the patient becomes comfortable often before one would believe such a thing possible.

As the patient improves, the mass felt on bimanual examination diminishes and becomes less tender. In one of my own patients, who admitted hospitalization for previous attacks, the masses diminished but did not entirely disappear, although symptomatic relief was complete.

Van Slyke removed the tube soon after an acute attack from a patient whom he had treated with sulfapyridine for acute salpingitis. The normal appearance of the tube was noteworthy. In another case in which I was interested, an inspection of the pelvis was made during an appendectomy three weeks after treatment with sulfathiazole for acute salpingitis. While the tubes themselves appeared normal, adhesions at their distal ends evidenced the accuracy of the earlier diagnosis. Evidently our decisions as to when and when not to perform salpingectomies will be modified in favor of greater conservatism as we gain experience in using chemotherapy.

It is evident that old residual pathology, such as adhesions and malpositions which cause pain, must be dealt with surgically as formerly.

Gonococcal Vaginitis of Children

Alfred Cohn and his associates, with whom I have been connected, recently reported the results of their long study of this troublesome

disease. In a large group of untreated children about 75 per cent recovered in 6 months or less. Vaginal suppositories of estrogens, which have been widely used, were found to give apparently good clinical results with smears which early became negative. That these results are more apparent than real is shown by the fact that cultures taken from the infected children so treated remained positive about as long, and as often, as in the untreated controls. Sulfapyridine given at 4 hour intervals four times per day cured about 90 per cent of a series of cases in which it was given. The dose for a child should not exceed 0.03 gram per pound of body weight daily, and should not total more than 2 grams per day.

As the newer drugs that we have discussed come into wider use, we may confidently expect a striking decline in the incidence of gonococcal infections throughout the country.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

OCTOBER 3—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes. ¶ Papers of the evening — Arterial Hypertension — a] Medical aspects, Edgar Allen, Consultant and Chief of a Section in the Division of Medicine, Mayo Clinic; b] Surgical aspects, Loyal Davis, Professor and Chairman, Division of Surgery, Northwestern University. ¶ Report on Election of Fellows.

OCTOBER 31—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The First Harvey Lecture, "Studies on Lymphocytic Choriomeningitis and Poliomyelitis," Charles Armstrong, Surgeon, U. S. Public Health Service, National Institute of Health.

SECTION MEETINGS

OCTOBER 1—*Section of Dermatology and Syphilology.* Presentations of Cases. ¶ General Discussion. ¶ Executive Session.

OCTOBER 4—*Section of Surgery.* Reading of the minutes. ¶ Presentation of cases—a] An unusual case of multiple fractures and dislocations, D. Rees Jensen. ¶ Discussion, Herbert M. Bergamini; b] Case illustrating combined traction-compression method for treatment of bicondylar fracture of the tiba, Robert A. Wise. ¶ Discussion, Condict W. Cutler, Jr.; c] Cases of fractures by muscular violence produced by convulsions after metrazol therapy for schizophrenia, Louis Carp. ¶ Discussion, Russell E. Blaisdell. ¶ Papers of the evening—a] Metacarpal-phalangeal dislocations, William Darrach; b] Convalescent care of the fracture patient, Robert H. Kennedy. ¶ General Discussion. ¶ Executive Session.

OCTOBER 8—*Section of Neurology and Psychiatry.* Presentation of case—A case of Klippel-Feil syndrome with asymbolia, Frances Cottington (by invitation). ¶ Discussion, Richard Brickner. ¶ Papers of the evening—a] Erroneous recognition (fausse reconnaissance), Clarence P. Oberndorf. ¶ Discussion, Nolan D. C. Lewis; b] Some observations on Ménière's syndrome and its relation to migraine and epilepsy, Miles Atkinson. ¶ Discussion, Harold G. Wolff; c] Electric shock therapy in mental disorders, S. Eugene Barrera (by invitation), L. Kalinowsky (by invitation), William A. Horowitz (by invitation). ¶ Discussion, Clarence O, Cheney, Karl M. Bowman.

OCTOBER 10—*Section of Pediatrics.* Program presented by members of the Mount Sinai Hospital Staff. ¶ Reading of the minutes. ¶ Papers of the evening—Symposium on suppurative and necrosuppurative bronchopneumonia in children —a] Pathogenesis and pathology, Alexander Thomas (by invitation); b] Clinical manifestations and complications, Herman Hennell; c] Roentgen features, Coleman B. Rabin; d] Treatment, George J. Ginandes (by invitation); e] Aerobic pulmonary abscess, Arthur S. W. Touroff; f] Pleural complications, Harold Neuhof. ¶ General discussion.

The Sections of Ophthalmology, Medicine, Genito-Urinary Surgery, Otolaryngology, Orthopedic Surgery and Obstetrics and Gynecology held no meetings in October because of conflict in dates with the Graduate Fortnight.

AFFILIATED SOCIETIES

OCTOBER 4—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* The Middleton Goldsmith Lecture was delivered by Dr. William Cramer on The Sex Hormones and the Endocrine Balance.

New York Roentgen Society. Because of conflict in dates with the Graduate Fortnight, this Society held no meeting in October.

DEATHS OF FELLOWS

CAMAC, CHARLES NICOLL BANCKER: 2703 Highland Avenue, Altadena, California: born in Philadelphia, Pennsylvania, August 6, 1868; died in California, September 27, 1940; received the degree of Bachelor of Arts from the University of Pennsylvania in 1892 and graduated in medicine from that institution in 1895; elected a Fellow of the Academy December 15, 1898 and served as a member of the Committee on Library from January 1909 to January 1914.

Dr. Camac was instructor of physiology at the University of Pennsylvania in 1895; at Cornell University Medical College he was director of the laboratory of clinical pathology 1899-1905, instructor of physical diagnosis, chief of the medical clinic, and lecturer in medicine 1905-1909, and professor of clinical medicine 1909-1910; and at the College of Physicians and Surgeons, Columbia University, he was assistant professor of clinical medicine from 1910 until his retirement. He was emeritus professor of medicine at the New York Polyclinic Hospital and Medical School and at one time was consulting physician to the New York City Hospital, and medical director and consulting physician to the Gouverneur and Bellevue Hospitals. He was a member of the Association of American Physicians, the Philadelphia Academy of Natural Sciences and the American Association for the Advancement of Science.

During the World War, Dr. Camac served as a medical officer in the United States Army reaching the grade of Lieutenant Colonel.

Dr. Camac was the author of a number of articles and books on the history of medicine, surgery and allied sciences.

COURTEN, HENRY CARLTON: 94-27 118 Street, Richmond Hill, New York; born in Palmyra, New York, May 3, 1879; died in Richmond Hill, October 15, 1940; received the degrees of A.B. and A.M. from Yale University; graduated in medicine from New York University and Bellevue Medical College in 1909; elected a Fellow of the Academy April 6, 1922.

Dr. Courten was director of orthopedics at the Jamaica Hospital, attending orthopedist to the Mary Immaculate and Lutheran Hospitals, consulting orthopedist to the Flushing, Rockaway Beach and Evangelical Deaconess Hospitals, and director of orthopedic surgery at the Queens General Hospital. He was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the Queensboro Surgical Society and the County and State Medical Societies.

HEAD, SIR HENRY: Hartley Court, England; born in London, August 4, 1861; died in Reading, October 9, 1940; attended the University of Halle, Germany; the German University of Prague, Czecho-Slovakia; and Trinity College; graduated in medicine from the University of Cambridge in 1892; elected an Honorary Fellow of the Academy November 18, 1926.

Sir Henry became a member of the Royal College of Surgeons in 1890 and a member of the Royal College of Physicians in 1894. Since 1900 he had been a fellow of the Royal College of Physicians.

As early as 1889 Sir Henry, working in Hering's laboratory in Prague, began his fundamental reports on the functions of the peripheral nerves. His investigations on the cutaneous distribution of pain and tenderness in visceral disease showing that the segmentation of the cutaneous areas affected by the different viscera corresponds with that belonging to the root ganglions of the spinal nerves are known to every medical student. These areas are now known as "Head's zones." In 1903 he made the unique experiment of dividing his own left radial and external cutaneous nerves. The observations of the loss and restoration of sensation which he experienced, together with extensive subsequent investigations, led to a new classification of sensory paths.

Sir Henry was at one time the editor of the medical publication "Brain," and the author of many medical papers and several volumes on neurology.